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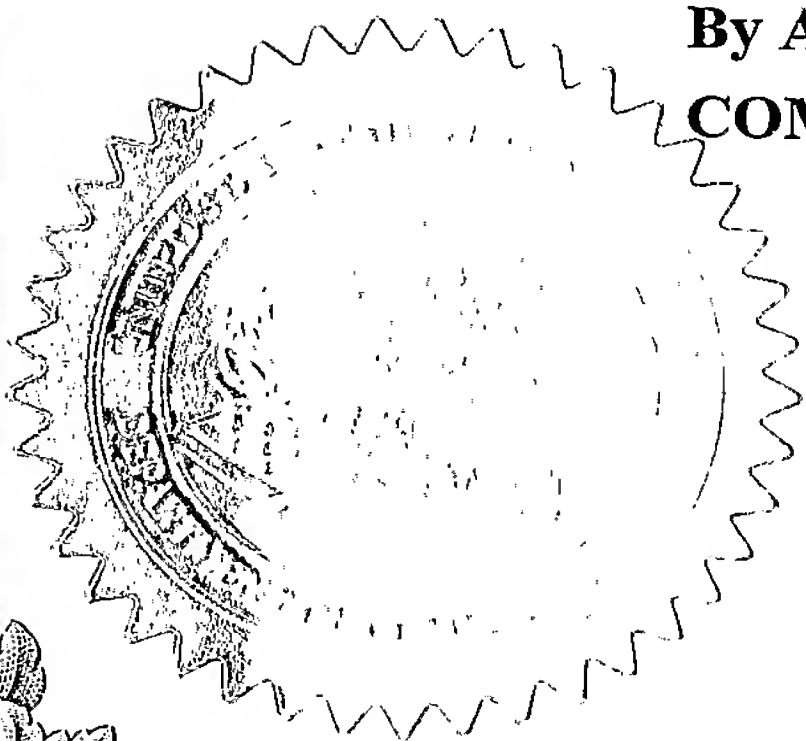
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Certifying Officer

TRANSMITTAL

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Title of Invention	Angiogenesis affecting polypeptides, proteins, and compositions, and methods of use thereof							
Application Number :								
Date :								
First Named Applicant:	Mats Hellstrom							
Confirmation Number:								
Attorney Docket Number:	72861							
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<table border="1"><tr><td>Submitted By:</td><td>Elec. Sign.</td><td>Sign. Capacity</td></tr><tr><td>Timothy Platt Registered Number: 43003</td><td>Timothy Platt</td><td>Agent</td></tr></table>			Submitted By:	Elec. Sign.	Sign. Capacity	Timothy Platt Registered Number: 43003	Timothy Platt	Agent
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Documents being submitted:	Files
us-request	72861-usrequ.xml us-request.dtd us-request.xsl
us-fee-sheet	72861-usfees.xml us-fee-sheet.xsl us-fee-sheet.dtd
application-body	Document2-trans.xml us-application-body.xsl application-body.dtd wipo.ent mathml2.dtd mathml2-qname-1.mod isoamsa.ent isoamsb.ent isoamsc.ent isoamsn.ent isoamso.ent isoamsr.ent isogr3.ent isomfrk.ent isomopf.ent isomscr.ent isotech.ent isobox.ent isocyr1.ent isocyr2.ent isodia.ent isolat1.ent isolat2.ent isonum.ent isopub.ent mmlextra.ent mmlalias.ent soextblx.dtd fig1.tif fig2.tif fig3.tif fig4.tif fig5.tif fig6.tif fig7.tif fig8.tif fig9.tif fig10.tif fig11.tif fig12.tif fig13.tif fig14.tif fig15.tif


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Comments

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Description

Angiogenesis affecting polypeptides, proteins, and compositions, and methods of use thereof

BACKGROUND OF INVENTION

[0001] Field of the Invention

[0002] The invention relates to polypeptides and proteins encoded thereby which are involved in vasculogenesis and/or angiogenesis. These agents may be targeted when producing materials and methods used in the diagnosis and therapy of angiogenesis-related conditions. The invention further relates to such diagnostic and therapeutic methods and agents.

[0003] Background of the Invention

[0004] Both vasculogenesis, the development of an interactive vascular system comprising arteries and veins, and angiogenesis, the generation of new blood vessels, play a role in embryonic development. In contrast, angiogenesis is

limited in a normal adult to the placenta, ovary, endometrium, and sites of wound healing. Angiogenesis, or its absence, plays an important role in the maintenance of a variety of pathological states. Some of these states are characterized by neovascularization, e.g., cancer, diabetic retinopathy, glaucoma, and age related macular degeneration. Others, e.g., stroke, infertility, heart disease, ulcers, and scleroderma, are diseases of angiogenic insufficiency.

[0005] Angiogenesis has a number of stages (see, e.g., Zhu and Witte, Invest New Drugs 17:195–212, 1999). The early stages of angiogenesis include endothelial cell protease production, migration of cells, and proliferation. The early stages also appear to require some growth factors, with VEGF, TGF- α and selected chemokines all putatively playing a role. Later stages of angiogenesis include population of the vessels with mural cells (pericytes or smooth muscle cells), basement membrane production, and the induction of vessel bed specializations. The final stages of vessel formation include what is known as remodelling wherein a forming vasculature becomes a stable, mature vessel bed. Thus, the process is highly dynamic, often requiring coordinated spatial and temporal waves of gene expression.

[0006] The complex angiogenesis process is subject to disruption through interference with one or more critical steps, and numerous disease states can result from or be exacerbated by the disruption. Unregulated angiogenesis can cause or worsen disease, for example, ocular neovascularization has been implicated as the most common cause of blindness and underlies the pathology of approximately 20 eye diseases. In certain previously existing conditions such as arthritis, newly formed capillary blood vessels invade the joints and destroy cartilage. In diabetes, new capillaries formed in the retina invade the vitreous humour, causing bleeding and blindness.

[0007] In addition to pathologies linked to unregulated angiogenesis, insufficient angiogenesis can also lead to undesirable results. Dead or damaged tissue can lead to numerous pathologies, revascularization of damaged tissues through a healthy, normal angiogenic process is essential to preventing further complications.

[0008] Therefore, new targets and treatments that inhibit or enhance angiogenesis are needed. Identification of more key factors involved in any stage of angiogenesis could lead to new diagnostic methods for pathologic conditions related to angiogenesis. Further, elucidation and understanding

of the key factors involved in angiogenesis could form the basis for new methods to investigate potential therapies for angiogenesis-related conditions.

SUMMARY OF INVENTION

[0009] In accordance with the objects outlined above, the present invention discloses eleven nucleic acid sequences and associated proteins which have key roles in vasculogenesis and/or angiogenesis. One object of the present invention is to present approaches for using the eleven novel factors as molecular targets for therapeutic intervention in angiogenesis-related disease states. It is a further object of the present invention to provide materials and methods that can be used to screen compounds for the ability to modulate angiogenesis or angiogenesis-related conditions.

[0010] Therapeutics specifically targeting the sequences and proteins identified herein are also provided as agents or compositions which modulate vasculogenesis or angiogenesis.

[0011] According to one embodiment of the invention, an isolated nucleic acid molecule according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 or a fragment or analogue thereof is provided which has the ability to stimu-

late or inhibit at least one biological activity selected from the group consisting of vasculogenesis, angiogenesis, vascular permeability, endothelial cell proliferation, endothelial cell differentiation, endothelial cell migration, and endothelial cell survival, or an isolated nucleic acid molecule which hybridizes to one of the foregoing sequences under stringent conditions. The invention is also directed to isolated nucleic acid molecules which hybridizes to a complement of a nucleic acid molecule described above, and an isolated siRNA molecule of at least 19 base pairs targeted to an isolated nucleic acid molecule described above.

[0012] According to a further embodiment of the invention, an expression vector comprising one of the novel nucleic acids is provided. The nucleic acid may be operatively associated with a regulatory nucleic acid controlling the expression of the polypeptide encoded by the nucleic acid.

[0013] The invention further comprises host cells genetically engineered to contain a nucleic acid as described above, or transfected by an expression vector described above.

[0014] According to a further embodiment of the invention, a method of treating an angiogenesis-related condition in a cell, group of cells, or organism is provided, comprising

administering an expression vector as described above to the cell, group of cells, or organism.

[0015] The invention further comprises antibodies with specific reactivity to the nucleic acid molecules described above. The antibodies may be polyclonal or monoclonal and may further comprise detectable labels, such as fluorescent labels.

[0016] According to a further embodiment of the invention, a transgenic, non-human animal is provided which has been genetically engineered to contain a transgene comprising a nucleic acid as described above, and animals which contain and express the transgene.

[0017] According to a further embodiment of the invention, a pharmaceutical composition is provided which comprises a nucleic acid sequence as described above. The compound may be administered to a cell, group of cells, or organism to affect vasculogenesis or angiogenesis. The effect may be to increase or decrease vasculogenesis or angiogenesis, and the method may be employed where the cells, group of cells, or organism has an angiogenesis-related disorder. Such angiogenesis-related disorders include cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertil-

ity, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis, and rheumatoid arthritis.

[0018] According to a further embodiment of the present invention, an isolated polypeptide comprising a sequence of amino acids substantially corresponding to the amino acid sequence in any one of SEQ ID NO:s 3, 5, 8, 10, 13, 15, 18, 20, 22, 25, 27, 30, 32, 35, 37, 40, 42, 45, 47, 50, 52, 55, and 57 or a fragment or analogue thereof is provided which has the ability to affect angiogenesis in a cell, a group of cells, or an organism.

[0019] The invention further comprises host cells genetically engineered to express a polypeptide as described above, as well as antibodies specifically reactive with the polypeptides. The antibody may be polyclonal or monoclonal, and may further comprise a detectable label such as fluorescence.

[0020] According to a further embodiment of the invention, a transgenic, non-human animal is provided which has been genetically engineered to contain a transgene comprising a nucleic acid which encodes a polypeptide as described above, and animals that contain and express the transgene.

[0021] The invention further provides pharmaceutical compositions comprising an isolated polypeptide as described above. The pharmaceutical composition may be administered to a cell, group of cells, or organism in order to affect vasculogenesis or angiogenesis therein. Vasculogenesis or angiogenesis may be increased or decreased. The cell, group of cells, or organism may have an angiogenesis-related disorder. Representative angiogenesis-related disorders are noted above.

[0022] According to a further embodiment of the invention, a method of detecting an angiogenesis-related transcript in a cell in a patient is provided, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56, wherein an an-

giogenesis-related transcript is detected where hybridization is detected. The polynucleotide may comprise a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56. The biological sample may be a tissue sample, or sample of isolated nucleic acids such as mRNA. According to this method, the nucleic acids may be amplified prior to contacting the biological sample with the polynucleotide. Further, the polynucleotide is immobilized on a solid surface.

[0023] According to a further embodiment of the present invention, a method of affecting at least one bioactivity selected from angiogenesis and vasculogenesis in a vertebrate organism is provided, where method comprises the step of administering an effective angiogenesis or vasculogenesis affecting amount of a nucleotide or polypeptide described herein to the organism. The organism may be mammal, such as mice, rats, rabbits, guinea pigs, cats, dogs, pigs, cows, monkeys, and humans. Vasculogenesis or angiogenesis may be enhanced, increased, inhibited, or decreased. This method may be used on organisms that have an angiogenesis-related disorder, such as those disorders described above.

[0024] According to a further embodiment of the invention, a transgenic increased angiogenesis laboratory animal is provided which comprises one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is upregulated. Transgenic decreased angiogenesis laboratory animals are also provided, which comprise one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is down regulated or absent.

[0025] The terms "angiogenesis-related condition" or "angiogenesis-related disease (state)" as used herein mean a condition which is marked by either an excess or a deficit of vessel development or which is improved by an increase or decrease in vessel development. Disorders associated with increased angiogenesis include, but are not limited to, cancer (including solid tumors, leukemias, and tumor metastases), benign tumors (including hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas), retinopathy, macular degeneration, and corneal ulceration. Pathological states linked to de-

creased angiogenesis or states which can improve with increased angiogenesis include, but are not limited to, ischemic heart disease, infertility, ulcers, scleradoma, (insufficient) wound healing, ischemia, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans (ASO), Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, and stroke. Other angiogenesis related diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, whether or not associated with diabetes, diseases with symptoms of chronic inflammation, such as inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

[0026] A "host cell" is a naturally occurring cell or a transformed cell that contains an expression vector and supports the replication or expression of the expression vector. Host cells may be cultured cells, explants, cells in vivo, and the like. Host cells may be prokaryotic cells such as *E. coli*, or eukaryotic cells such as yeast, insect, amphibian, or mam-

malian cells such as CHO, HeLa, and the like (see, e.g., the American Type Culture Collection catalog or web site, www.atcc.org).

[0027] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0028] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, gamma-carboxyglutamate, and O-phosphoserine. "Amino acid analogs" refers to compounds that have the same basic chemical structure as a naturally occurring amino acid. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a

naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0029] The term "conservative modifications" or "conservatively modified variants" as used herein applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of

the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual probe sequences.

[0030] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known

in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0031] As used herein, "label" or "detectable moiety" refers to a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. Examples of such labels include ^{32}P , fluorescent dyes, electron-dense reagents, enzymes, biotin, digoxigenin, or haptens and proteins which can be made detectable, e.g., by incorporating a radiolabel into the peptide or used to detect antibodies specifically reactive with the peptide.

[0032] As used herein, "vector" or "expression vector" refers to a nucleic acid construct, generated recombinantly or synthetically, with a series of specified nucleic acid elements that permit transcription of a particular nucleic acid in a host cell. The expression vector can be part of a plasmid, virus, or nucleic acid fragment. Typically, the expression vector includes a nucleic acid to be transcribed operably linked to a promoter.

[0033] The phrase "stringent hybridization conditions" as used herein refers to conditions under which sequences will hybridize. Stringent conditions are sequence-dependent and

will be different in different circumstances. Skilled workers have access to significant amounts of descriptive material detailing reaction conditions that are appropriate for a given sequence. One example is Innis et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, Inc. N.Y.).

[0034] As used herein, the terms "inhibitors," "activators," and "modulators" of angiogenic polynucleotide and polypeptide sequences and angiogenic activity refer to inhibitory, activating, or modulating molecules. "Inhibitors" are compounds that, e.g., bind to, partially or totally block activity, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity or expression of angiogenesis proteins, e.g., antagonists. "Activators" are compounds that increase, open, activate, facilitate, enhance activation, sensitize, agonize, or up regulate angiogenesis protein activity. Inhibitors, activators, or modulators include genetically modified versions of angiogenesis proteins, e.g., versions with altered activity, as well as naturally occurring and synthetic ligands, antagonists, agonists, antibodies, small chemical molecules and the like. Assays for inhibitors and activators include, e.g., expressing the angiogenic protein in vitro, in cells, or cell mem-

branes, applying putative modulator compounds, and then determining the functional effects on activity, as described above.

BRIEF DESCRIPTION OF DRAWINGS

[0035] Figure 1 shows a ratio–ratio plot with the \log_2 expression ratio of genes in a cDNA library when compared to embryonic brain endothelial cell portion versus embryonic brain left over portion and adult brain endothelial cell portion versus adult brain left over portion;

[0036] Figure 2 shows a ratio–intensity plot with average intensity versus \log_2 expression ratio of genes in a cDNA library when compared to embryonic brain, heart, and skin endothelial cell versus left over embryonic portions and all adult endothelial cells and left over portions;

[0037] Figure 3 schematically depicts microarray data for gene HUP8001J6;

[0038] Figure 4 shows a wild type zebrafish embryo at 28 hpf;

[0039] Figure 5 shows a HUP8001J6 morphant embryo at 28 hpf;

[0040] Figure 6 shows a wild type zebrafish embryo at 56 hpf;

[0041] Figure 7 shows a HUP8001J6 morphant embryo at 56 hpf;

[0042] Figure 8 shows a wild type zebrafish at 48–56 hpf;

- [0043] Figure 9 shows a HUP8001J6 morphant embryo at 48–56 hpf;
- [0044] Figure 10 schematically depicts microarray data for gene HUP8001K17;
- [0045] Figure 11 shows a HUP8001K17 morphant embryo at 28 hpf;
- [0046] Figure 12 shows a HUP8001K17 morphant embryo at 56 hpf;
- [0047] Figure 13 shows a HUP8001K17 morphant embryo at 48–56 hpf;
- [0048] Figure 14 schematically depicts microarray data for gene HUP8001K21;
- [0049] Figure 15 shows a HUP8001K21 morphant embryo at 28 hpf;
- [0050] Figure 16 shows a HUP8001K21 morphant embryo at 56 hpf;
- [0051] Figure 17 shows a HUP8001K21 morphant embryo at 48–56 hpf;
- [0052] Figure 18 schematically depicts microarray data for gene HUP8003D24;
- [0053] Figure 19 shows a HUP8003D24 morphant embryo at 48–56 hpf;
- [0054] Figure 20 schematically depicts microarray data for gene

HUP8004N1;

[0055] Figure 21 shows a HUP8004N1 morphant embryo at 28 hpf;

[0056] Figure 22 shows a HUP8004N1 morphant embryo at 56 hpf;

[0057] Figure 23 shows a HUP8004N1 morphant embryo at 48–56 hpf;

[0058] Figure 24 schematically depicts microarray data for gene HUP8010A10;

[0059] Figure 25 shows a HUP8010A10 morphant embryo at 28 hpf;

[0060] Figure 26 shows a HUP8010A10 morphant embryo at 56 hpf;

[0061] Figure 27 shows a HUP8010A10 morphant embryo at 48–56 hpf;

[0062] Figure 28 schematically depicts microarray data for gene NOC8003L17;

[0063] Figure 29 shows a NOC8003L17 morphant embryo at 28 hpf;

[0064] Figure 30 shows a NOC8003L17 morphant embryo at 56 hpf;

[0065] Figure 31 shows a NOC8003L17 morphant embryo at 48–56 hpf;

- [0066] Figure 32 schematically depicts microarray data for gene NOC8009C9;
- [0067] Figure 33 shows a NOC8009C9 morphant embryo at 28 hpf;
- [0068] Figure 34 shows a NOC8009C9 morphant embryo at 56 hpf;
- [0069] Figure 35 shows a NOC8009C9 morphant embryo at 48–56 hpf;
- [0070] Figure 36 schematically depicts microarray data for gene NOC8009G23;
- [0071] Figure 37 shows a NOC8009G23 morphant embryo at 28 hpf;
- [0072] Figure 38 shows a NOC8009G23 morphant embryo at 56 hpf;
- [0073] Figure 39 shows a NOC8009G23 morphant embryo at 48–56 hpf;
- [0074] Figure 40 schematically depicts microarray data for gene OJC8003C9;
- [0075] Figure 41 shows a OJC8003C9 morphant embryo at 28 hpf;
- [0076] Figure 42 shows a OJC8003C9 morphant embryo at 56 hpf;
- [0077] Figure 43 shows a OJC8003C9 morphant embryo at 48–56

hpf;

[0078] Figure 44 schematically depicts microarray data for gene OJC8009J7;

[0079] Figure 45 shows a OJC8009J7 morphant embryo at 28 hpf;

[0080] Figure 46 shows a OJC8009J7 morphant embryo at 56 hpf; and

[0081] Figure 47 shows a OJC8009J7 morphant embryo at 48–56 hpf.

DETAILED DESCRIPTION

[0082] While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention. Materials, the synthesis of which are not specifically described, are either commercially available or can be prepared using methods well known to those of skill in the art. Except as otherwise noted, all amounts including quantities, percentages, portions, and proportions, are understood to be modified by the word "about", and

amounts are not intended to indicate significant digits. Except as otherwise noted, the articles "a", "an", and "the" mean "one or more". All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

[0083] Identification of Candidate Genes

[0084] A cDNA Library was prepared by collecting the mRNA from purely isolated adult and embryonic mice vascular fragments. The collected mRNA was used to develop cDNA libraries with a broad coverage of genes expressed in the vasculature. Because of the variety in mouse age, the vascular genes represented those active at different times and in different situations in the vasculature.

[0085] After creation of the cDNA library, microarrays were created by printing DNA from the cDNA library onto a solid support as known in the art. The microarrays were used to reveal the gene candidates through gene expression profiling. Select tissues from adult and E 18.5 embryonic mice were collected. Tissue selection was based on the amount and purity of RNA available for extraction. After tissues were removed, they were separated into two portions using antibodies or lectins. The first portion, the en-

dothelial cell fraction or EC, contained endothelial cells as well as pericytes and vascular smooth muscle cells which are tightly associated with the vascular fragments. The second portion, also referred to as the left over portion or LO, were those cells remaining after the EC was isolated.

0086] From adult mice, brain and heart tissues were used, both the EC and LO of each. From embryonic mice, brain, heart, and skin, both EC and LO of each, were utilized. The RNA from each fraction was extracted. A common reference RNA (Universal Mouse Reference RNA; Stratagene, Inc.) was employed at this stage for reference purposes. The isolated RNA and the reference RNA were reverse transcribed then amplified twice through two rounds of anti-sense RNA amplification. The isolated RNA was labelled with the fluorophore cyanine-3 and the reference RNA with cyanine-5.

0087] After labelling, the RNA was assayed through hybridization with the microarrays described above. The hybridized microarrays were scanned and image analysis used to process the experimental data. Normalizing the data through a signal intensity-based normalization algorithm allowed for statistical evaluation of differentially expressed genes. Genes exhibiting differential expression

were selected for further analysis.

[0088] Selection of Genes with Differential Expression

[0089] Using data collected as described above, certain genes were designated as selectively expressed in blood vessels. This was based on comparisons between adult and embryonic EC and LO values. Figure 1 shows a ratio-ratio plot of the data values obtained through comparisons between embryonic brain EC and LO genes and between adult brain EC and LO genes. A comparison of total adult EC with total embryonic EC was also conducted, data not shown. Data points represented with "DT1 candidates" or "DT2 candidates" were generally upregulated ($>0 \log_2$ expression ratio).

[0090] Other genes were designated as selectively expressed during angiogenesis through a different comparison of data. The total embryonic EC portion (i.e., brain, heart, and skin EC portions) was compared to all remaining tissues, including the total embryonic LO portion and all adult RNA (EC and LO of both brain and heart). Figure 2 shows a ratio-intensity plot with the average intensity versus \log_2 expression ratio of all genes. The data points marked DT3 candidates and DT4 candidates are those genes shown to be up regulated through this selective

analysis. A comparison was also undertaken to analyze all EC portions versus all LO portions, data not shown.

[0091] A total of eleven genes of interest were selected for further analysis. Specific expression data for each gene follows throughout and includes a graph showing that gene's expression profile. Tables are used to show the intensity of the microarray signal, the \log_2 expression ratio, p-value, and rank (rank given only for certain fields). The highest rank was awarded to the gene with the highest expression ratio value, the lowest rank was assigned to the gene with the lowest expression value, based on expression ratio values. P-values are given as a value from zero to one. Values close to one indicate a gene that is upregulated, whereas values close to zero indicate a statistically down regulated gene. A statistically significant p-value of 0.05 corresponds to a p-value of 0.05 or 0.95.

[0092] For graphs, tables, and text the abbreviation eec/r refers to embryonic EC portions versus all remaining portions, ec/lo refers to all EC portions versus all LO portions, abeclo refers to adult brain EC portion versus adult brain LO portion, abecebec refers to adult brain EC portion versus embryonic brain EC portion, aheclo refers to adult heart EC portion versus adult heart LO portion, ebeclo

refers to embryonic brain EC portion versus embryonic brain LO portion, eheclo refers to embryonic heart EC portion versus embryonic heart LO portion, and eseclo refers to embryonic skin EC portion versus embryonic skin LO portion..

[0093] Evaluation of Selected Genes

[0094] Further analysis of selected genes was conducted through knockdown technology in zebrafish. The process involves the use of specific antisense oligonucleotides that block translation from targeted mRNA molecule(s). This allows for inhibition of the gene of interest and allows for a determination of gene function in the development and health of the zebrafish. Zebrafish share genes for vertebrate functions with mammalian vertebrates such as mice and humans. Studies have demonstrated that organ and/or tissue development in zebrafish can reliably predict effects in humans (See, inter alia, Shin and Fishman, From zebrafish to humans: Modular medical models, Ann. Rev. Genomics and Human Genet. 2002: 3: 311-340; Clark et al., An oligonucleotide fingerprint normalized and expressed sequence tag characterized zebrafish library, Genome Res 2001 Sep;11(9):1594-602. Because of their rapid external development, zebrafish embryo develop-

ment can be easily monitored and analyzed. The presence of a yolk sac helps provide data from the development of a critically deficient embryo further than that possible with other research organisms, such as mice.

0095] To prepare the embryos, the zebrafish homolog of the target gene was identified. Then, a specific morpholino phosphorodiamidate oligonucleotide was designed to match the AUG initiation codon or splice acceptor/donor site of the target gene. To create a stock solution of morpholino, pellets containing 100 nmoles of the phosphorodiamidate oligonucleotides were dissolved in 33.3 μ l milli-Q water, giving a concentration of 25 mg/ml, and stored at -20°C . To create injection solution, 8 μ l of the stock solution was added to 92 μ l of sterile-filtered 1X Danieu buffer (58 mM NaCl, 0.7 mM KCl, 0.4 mM MgSO_4 , 0.6 mM $\text{Ca}(\text{NO}_3)_2$, 5 mM HEPES, pH 7.6) supplemented with 15mM Tris-Cl, pH 8.0. The 2 mg/ml injection solution was also stored at -20°C .

0096] During injection, the materials and embryos were maintained at approximately 28°C . Injection needles were calibrated so that injection times could optimally be within a range of 100–600 msec. Embryos from the one cell stage to the early eight cell stage were used. The morpholinos

were microinjected into the yolk sac. Specific injection volumes, or effective dose of the morpholino, are described below. Typical initial doses included 3, 6, and 12 ng (1.5, 3, and 6 nl, respectively). Toxicity at the 3 nl dose resulted in subsequent doses of 0.5, 1, and 2 ng (1, 2, and 4 nl, respectively). Approximately 40 embryos were injected at each dose level, and approximately 40 embryos were retained as non-injected controls.

0097] After the morpholinos were injected into fertilized egg cells, the embryos engineered to have a knockdown of the specific gene were allowed to develop (See Nasevicius and Ekker, Effective targeted gene "knockdown" in zebrafish, Nature Genetics vol 26, October 2000.). The embryos were monitored throughout development, both by examining morphology and undertaking specific analysis and assays of developing tissues.

0098] In addition to single morpholino injections, double morpholino injections were performed as well. Specific injection volumes for double injections are described below. At the end of the first post-injection day, with embryos at the blastula or gastrula stage, propyl thioracil (PTU) 2x solution was added to the embryos, doubling their suspension volume. 48 hours post fertilization (hpf) the dou-

ble injected embryos were fixed with cadherin 5 (cdh5) for in situ hybridization.

0099] When 20% or more of the double injected embryos displayed low effect defects in the vasculature observed with cdh5, or when 10% or more of the embryos displayed medium or high effect defects, then microangiopathy and in situ hybridization with fli-1, flk-1, flt-4, tie-1, tie-2, and cdh5 were conducted. At least 120 embryos were administered the double morpholino dose, of which at least 100 were harvested at 24 hpf for in situ hybridization with the above-noted molecular markers. Remaining embryos were used for microangiopathy.

0100] Data specific to the evaluation of each of the eleven targets are described below. In general, the morphology observations conducted at 24-28 hpf included an indication of whether the embryos exhibited general delay relative to control embryos. Further, cell death type and degree were recorded, general embryo shape and brain morphology were recorded as well. Finally, yolk sac edema, if present, was evaluated and recorded, as was heart morphology.

0101] Also, at approximately 24 hpf, double morpholino embryos were evaluated for in situ hybridization of fli-1, flk-1, flt-4, tie-1, tie-2, and cdh5. Overall morphology and

the degree of reduction of staining in the intersegmental vessels as compared to control embryos, correlating to a percentage of lost expression, were noted. Those embryos showing a loss of 1–35% of intersegmental expression were considered to have a low effect, those embryos showing a loss of 36–70% of intersegmental expression were considered to have a medium effect, and those embryos showing a loss of 71–100% of intersegmental expression were considered to have a high effect.

0102] At 48–56 hpf various parameters were reviewed and recorded, such as general embryo shape, degree of cell death, blood circulation, and heart morphology. For the embryos fixed with cdh5, staining was evaluated throughout the vasculature as described immediately above.

0103] Microangiopathy was also evaluated at 48hpf in double morpholino embryos. In order to observe the blood vessels, the embryos were transferred into a tricaine solution and the sinus venosa/common cardinal vein was injected with 10 μ l FITC–Dextran solution (2,000,000 Da, 20 mg/ml).

0104] Gene HUP8001J6

0105] The gene having the sequence shown in SEQ ID NO:1 was identified as selectively expressed during angiogenesis

based on microarray data, see Figure 3. Specific data are given below in Table 1. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:2) and the human homolog (SEQ ID NO:4) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 3 and 5, respectively.

0106] Based on this expression profile, the gene was further analyzed in zebrafish embryos. Two corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz265 and sz266, each targeted to one of the zebrafish genes. Six (6) ng of sz265 morpholino and 2 ng of sz266 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

0107] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe fli-1 revealed that 13% of the 16 morphant embryos assayed had high effects, that is, loss of 71-100% of intersegmental expression. The probe flk-1, VEGF receptor 2, indicated that 7% of the 15 morphants reviewed had high effects. When analyzed through the probe tie-1, all 15 morphants observed were normal. The probe cdh5, VE

cadherin, indicated that all 23 morphants observed were normal. The probe flt-4, VEGF receptor 3, indicated that all 15 morphants observed were normal. And the probe tie-2 showed all 15 observed morphants as normal. Table 2 summarizes this data.

0108] At 28 hpf embryos were observed morphologically. Both the wild type embryos, used as control, and the morphant embryos observed showed normal morphology. Figures 4 and 5 show the wild type and morphant embryos at 28 hpf, respectively. At 56 hpf the embryos were again observed, a wild type embryo is shown in Figure 6 and a morphant embryo in Figure 7. As highlighted by an arrow in the representative embryo of Figure 7, 82% of the 56 morphant embryos showed severe yolk sac edema. Further, 70% showed severely reduced blood flow and 14% showed reduced intersegmental blood flow.

0109] Additional analyses were conducted on 48–56 hpf morphant embryos. A primary in situ hybridization screen with cdh5 on 22 morphants revealed that 18% had reduced intersegmental expression, at a low effect level, whereas the remaining 82% were normal. Microangiography on 22 morphants was used to locate the presence of FITC–Dextran in various regions of the embryo. No FITC–

Dextran was observed in the heart, head, nor was there any leaky vasculature. 14% of the morphants showed high effects of reduced intersegmental vasculature, and another 14% showed low effects of the same. Thus, 28% were affected by some changes to the intersegmental vasculature and 72% appeared normal. A wild type embryo at this time stage is shown in Figure 8, whereas Figure 9 shows a representative of the 48–56 hpf embryos analyzed. The arrow points to an area of reduced intersegmental vasculature.

0110] Gene HUP8001K17

0111] The gene having the sequence shown in SEQ ID NO:6 was identified as selectively expressed in blood vessels based on microarray data, see Figure 10. Specific data are given below in Table 3. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:7) and the human homolog (SEQ ID NO:9) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 8 and 10, respectively.

0112] Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two different morpholinos were prepared, sz143 and sz144, each targeted to the

zebrafish gene. Different amounts of morpholinos were administered as described below. The predetermined amount of each morpholino was administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf secondary in situ hybridization screens with six different probes were conducted.

- 0113] One screen was performed on embryos that received 1 ng of sz143 morpholino and 4 ng of sz144 morpholino. Four probes specifically selected to analyze axial and intersegmental vessel expression revealed the following: using the *fli-1* probe, 6% of the 17 embryos analyzed had medium intersegmental expression effects. Another 18% had high effects. The probe *flk-1*, VEGF receptor 2, indicated that 20% of the 15 morphants reviewed had medium and 13% had high effects. When analyzed through the probe *tie-1*, 63% of the 16 morphants observed had high effects. The probe *cdh5*, VE cadherin, indicated that 4% of the 24 morphants observed had medium effects, and another 4% had high effects. The probe *flt-4*, VEGF receptor 3, indicated that all 14 morphants observed were normal, and the probe *tie-2* showed all 18 observed morphants as normal.
- 0114] The other screen was performed on embryos that received 1.5 ng of sz143 morpholino and 6 ng of sz144 mor-

pholino. The probe fli-1 indicated that 42% of the 12 morphants analyzed had high effects. The flk-1 probe demonstrated that 23% of the 13 morphants observed had high effects. The tie-1 probe revealed 54% of 13 morphants had high effects. The probe cdh5 indicated that 15% of 27 morphants had medium effects and another 11% had high effects. The probe flt-4 indicated that all 14 morphants observed were normal. And the probe tie-2, showed all 18 observed morphants as normal. Table 4 summarizes this data.

0115] At 28 hpf embryos were observed morphologically. The wild type embryos, used as control, showed normal morphology as expected. As indicated previously, Figure 4 shows a wild type embryo at 28 hpf. The morphant embryos received a 1.5 ng dose of sz143 and a 6 ng dose of sz144, all did not exhibit normal morphology. A representative embryo is shown in Figure 11. Twenty embryos were observed, 50% of them showed a curly down body, indicated by the arrowhead in Figure 11, with yolk tube extension, indicated with a short arrow. Mild cell death was observed in 60% of the embryos, as shown by the long arrow in Figure 11. Finally, 50% of the embryos had yolk cell edema.

0116] At 56 hpf embryos were again observed, for reference a wild type embryo is shown in Figure 6. A morphant at the corresponding stage is shown in Figure 12. Twenty (20) embryos were observed, 90% had a curly down body as shown by the long arrow in Figure 12, with reduced head as indicated by the short arrow. Pericardial edema, shown by the arrowhead, was observed in 90% of the embryos and reduced blood flow was also seen in 90% of the embryos.

0117] Additional analyses were conducted on 48–56 hpf morphant embryos. A primary in situ hybridization screen with *cdh5* on 18 morphants which had received 1 ng sz143 and 3 ng sz144 revealed that 28% had reduced intersegmental expression, at a low effect level, with short and curly tails. The remaining 72% were normal. The same in situ hybridization screen was conducted using 11 morphants which had received 2 ng sz143 and 6 ng sz144. This revealed that 9% had reduced intersegmental expression, at a low effect level, with very short tails. The remaining 91% were normal.

0118] Microangiography on 26 morphants which had received 1.5 ng of sz143 and 6 ng of sz144 was used to locate the presence of FITC–Dextran in various regions of the em–

bryo. No FITC-Dextran was observed in the heart, but 31% of the embryos had FITC-Dextran in the head and heart. A total of 27% of the morphants had reduced intersegmental vasculature, and leaky vasculature was observed in 35% of the embryos. Only 42% of the embryos appeared normal. The combined percentages are greater than 100% since some embryos exhibited more than one non-normal feature. Figure 13 shows a representative of the 48–56 hpf embryos analyzed. The arrow points to an area of reduced intersegmental vasculature, and the arrowhead indicates a point of leaky vasculature. For reference, a wild type embryo at this time stage is shown in Figure 8. The experimental data reveal that the gene is expressed by scattered cells in many organs, but most clearly seen in the CNS.

0119] Gene HUP8001K21

0120] The gene having the sequence shown in SEQ ID NO:11 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 14. Specific data are given below in Table 5. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:12) and the human homolog (SEQ ID NO:14) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 13 and 15, respectively.

0121] Based on this expression profile, the gene was further analyzed in zebrafish embryos. Two corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz257 and sz258, each targeted to one of the zebrafish genes. Twelve (12) ng of sz257 morpholino and 12 ng of sz258 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

0122] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe fli-1 revealed that all of the 15 morphant embryos assayed were normal. The probe flk-1 indicated that 13% of the 16 morphants reviewed had low effects and 6% had high effects. When analyzed through the probe tie-1, all 15 morphants observed were normal. The probe cdh5 indicated that all 26 morphants observed were normal. The probe flt-4 indicated that all 17 morphants observed were normal, the probe tie-2 showed all 20 observed morphants as normal. Table 6 summarizes the data.

0123] At 28 hpf embryos were observed morphologically. Figure 15 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, yolk sac edema was observed in

47% of the 55 morphants analyzed. At 56 hpf a total of 53 embryos were observed, a representative morphant embryo is shown in Figure 16. As highlighted by the long arrow, expanded hindbrain was found in 34% of embryos. Yolk sac edema, shown by a short arrow, was also observed in 58% of embryos. An arrowhead points out the location checked for pericardial edema; it was not observed.

0124] Additional analyses were conducted on 48–56 hpf morphant embryos. A primary in situ hybridization screen with *cdh5* on 20 morphants showed all as normal. Microangiography on 31 morphants was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 17. Of the 31 embryos, 19% had FITC–Dextran in the heart but none had it in the heart and the head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 17. High effects were observed in 19% of the embryos, medium effects in 13% and low effects in 29%. No leaky vasculature was observed. Normal embryos accounted for 19% of the sample.

0125] HUP8003D24

0126] The gene having the sequence shown in SEQ ID NO:16 was identified as selectively expressed during angiogenesis

based on microarray data, see Figure 18. Specific data are given below in Table 7. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:17) and two human homologs (SEQ ID NO:s19 and 21) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 18, 20, and 22, respectively.

0127] Based on this expression profile, the gene was further analyzed in zebrafish embryos. Three corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz185 and sz186, which were targeted to the three zebrafish genes. For the lower dose group, 3ng of sz185 morpholino and 6ng of sz186 morpholino were administered to each fertilized egg. For the double dose group, 6ng of sz185 morpholino and 12ng of sz186 morpholino were administered. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

0128] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In the lower dose group, the probe fli-1 revealed that 18% of the 11 morphant embryos assayed had medium effects, i.e., 36-70% loss of intersegmental expression, and 18% had high effects. The probe flk-1 indicated that 36% of the 11

morphants reviewed had high effects. The probe tie-1 indicated that 29% of the 14 morphants observed had high effects. The probe cdh5 indicated 31% of the 16 morphants observed had high effects, and 31% had medium effects. The probe flt-4 indicated that all 16 morphants observed were normal, and the probe tie-2 indicated that all 15 morphants observed were normal.

0129] In the higher dose group, the probe fli-1 revealed that 33% of the 3 morphant embryos assayed had low effects and 33% had medium effects. The probe flk-1 indicated that 100%, or both of the 2 morphants reviewed, had medium effects. The probe cdh5 indicated 100%, all 7 of the morphants observed had high effects. The probe flt-4 indicated that all 3 morphants observed were normal, and the probe tie-2 indicated that all 7 morphants observed were normal. Table 8 summarizes this data.

0130] At 28 hpf embryos were observed morphologically. Cell death was observed in 70% of the 66 embryos observed. Yolk sac edema was observed in 29% of the morphants. At 56 hpf a total of 66 embryos were observed for phenotypic characteristics. Yolk sac edema was observed in 42% of embryos, 35% showed reduced IS blood flow and 26% showed reduced blood flow.

- 0131] Additional analyses were conducted on 48–56 hpf morphant embryos.
- 0132] A primary in situ hybridization screen with *cdh5* on 21 morphants receiving the lower doses noted above (3ng sz185, 6ng sz86) showed 52% as normal. Low effects of reduced intersegmental expression were seen in 43% of the embryos, and medium effects in 5%. Embryos receiving the double doses (6ng sz185, 12ng sz186), when viewed at the 48–56 hpf stage revealed 74% of the that the 23 embryos observed were normal. Low effects of reduced intersegmental expression were observed in 22% and medium effects in 4% of the embryos.
- 0133] Microangiography on morphants given the lower dose of morpholinos (3ng sz185, 6ng sz186) was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 19. Of the 33 embryos, none had FITC–Dextran in the heart, or the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 19. High effects were observed in 6% of the embryos, medium effects in 15% and low effects in 36%. No leaky vasculature was observed. Normal embryos accounted for 43% of the sample.
- 134] The data reveal that the gene is expressed in many loca–

tions, such as vessels and epithelial structures in the kidneys as well as in large vessels, megakaryocytes, in heart valves and in the skin epithelium.

0135] Gene HUP8004N1

0136] The gene having the sequence shown in SEQ ID NO:23 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 20. Specific data are given below in Table 9. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:24) and the human homolog (SEQ ID NO:26) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 25 and 27, respectively.

0137] Based on this expression profile, the gene was further analyzed in zebrafish embryos. Two corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz223 and sz224, each targeted to one of the zebrafish genes. Two dosing strategies were employed. The first dose group received 2ng of sz223 morpholino and 1ng of sz224 morpholino in each fertilized egg. The second dose group received 1ng of sz223 morpholino and 0.5ng of sz224 morpholino in each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different

probes was conducted.

0138] Intersegmental expression in embryos from the second dose group (1ng sz223, 0.5ng sz224) was analyzed in the assay and results differed somewhat based on the probe used. The probe fli-1 revealed that 7% of the 15 morphant embryos assayed had low effects, and 7% had high effects. The probe flk-1 indicated that 7% of the 14 morphants reviewed had high effects. The probe tie-1 indicated that 7% of the 14 morphants observed had low effects, and 7% had high effects. The probe cdh5 indicated that 8% of the 26 morphants observed had medium effects. The probe flt-4 indicated that all 15 morphants observed were normal, and the probe tie-2 indicated that all 15 morphants observed were normal. Table 10 summarizes this data.

0139] At 28 hpf embryos were observed morphologically. Figure 21 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, yolk sac edema was observed in 56% of the 59 morphants studied. At 56 hpf a total of 20 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure22. As indicated by the arrow, pericardial edema was observed in 35% of embryos, 65% had a blood pool in the yolk, also indicated by the arrow, and 30% showed reduced IS blood

flow.

0140] Additional analyses were conducted on 48–56 hpf morphant embryos from the second dose group. A primary in situ hybridization screen with *cdh5* on 22 morphants showed all as normal. Microangiography on 30 second dose group morphants was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 23. Of the 30 embryos, 13% had FITC–Dextran in the heart, and 3% in the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 23. High effects were observed in 7% of the embryos and low effects in 20%. No leaky vasculature was observed. Normal embryos accounted for 57% of the sample.

0141] The data reveal that the gene is expressed in specific endothelium. In kidneys, it is expressed by certain vessels and some other epithelial structures. There is also some expression in the liver.

0142] Gene HUP8010A10

0143] The gene having the sequence shown in SEQ ID NO:28 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 24. Specific data are given below in Table 11. Using sequence and annotation

databases the equivalent gene in mice (SEQ ID NO:29) and the human homolog (SEQ ID NO:31) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 30 and 32, respectively.

0144] Based on this expression profile, the gene was further analyzed in zebrafish embryos. A corresponding zebrafish genes was identified for targeting. Two morpholinos were prepared, sz267 and sz268, each targeted to one of the zebrafish genes. In a first dosage group, 4ng of sz267 morpholino and 2ng of sz268 morpholino were administered to each fertilized egg. In a second dosage group, 6ng of sz267 morpholino and 3ng of sz268 morpholino were administered. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

0145] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In the first dose group (4ng sz267, 2ng sz268), the probe fli-1 revealed that 13% of the 15 morphant embryos assayed had high effects. The probe flk-1 indicated that 33% of the 15 morphants reviewed had low effects and 20% had high effects. The probe tie-1 indicated that all 17 morphants observed were normal. The probe cdh5 indicated

that 8% of the 25 morphants observed had high effects. The probe flt-4 indicated that all 13 morphants observed were normal, and the probe tie-2 indicated that all 16 morphants observed were normal.

0146] In the second dose group (6ng sz267, 3ng sz268), the probe fli-1 revealed that 25% of the 16 morphant embryos assayed had low effects, and 19% had high effects. The probe flk-1 indicated that 33% of the 6 morphants reviewed had low effects. The probe tie-1 indicated that 67% of the 15 morphants observed had high effects. The probe cdh5 indicated that 21% of the 24 morphants observed had low effects, 13% had medium effects, and 29% had high effects. The probe flt-4 indicated that all 15 morphants observed were normal, and the probe tie-2 indicated that all 15 morphants observed were normal. Table 12 summarizes this data.

0147] At 28 hpf embryos were observed morphologically. Figure 25 shows a representative morphant embryo at 28 hpf. Cell death in the head was observed in 47% of the 61 embryos observed, as indicated by the arrow in Figure 25. The arrowhead indicates expanded hindbrain, which was seen in 51% of embryos. Mild yolk sac edema was observed in 21% of the morphants. At 56 hpf a total of 59

embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 26. The arrow indicates expanded hindbrain, which was seen in 44% of embryos. Mild yolk sac edema was observed in 29% of the morphants and is indicated by the arrowhead. Reduced IS blood flow was noted in 14% of the embryos, and reduced blood flow was found in 17% of the embryos.

148] Additional analyses were conducted on 48–56 hpf morphant embryos from the second dose group. A primary in situ hybridization screen with *cdh5* on 19 morphants showed 68% as normal. Low effects of reduced intersegmental expression were seen in 32% of the embryos. Microangiography on morphants was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 27. Of the 32 embryos, none had FITC–Dextran in the heart, or the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 27. High effects were observed in 6% of the embryos, medium effects in 3% and low effects in 34%. No leaky vasculature was observed. Normal embryos accounted for 56% of the sample.

149] Gene NOC8003L17

150] The gene having the sequence shown in SEQ ID NO:33 was

identified as selectively expressed in blood vessels based on microarray data, see Figure 28. Specific data are given below in Table 13. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:34) and the human homolog (SEQ ID NO:36) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 35 and 37, respectively.

151] Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz180 and sz181, each targeted to the zebrafish gene. In a first dose group, 12ng of sz180 and 1ng of sz181 were administered to each fertilized egg. In a second dose group, 12ng of sz180 and 2ng of sz181 were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

152] Intersegmental expression in embryos from the first dose group was analyzed in the assay and results differed somewhat based on the probe used. The probe fli-1 revealed that 40 of the 15 morphant embryos assayed had high effects. The probe flk-1 indicated that all 7 of the

morphants reviewed were normal. The probe tie-1 indicated that all 15 morphants observed were normal. The probe cdh5 indicated that 15% of the 20 morphants observed had low effects, as well as 5% with medium effects and 30% with high effects. The probe flt-4 indicated that all 11 morphants observed were normal, and the probe tie-2 indicated that all 16 morphants observed were normal. Table 14 summarizes this data.

0153] At 28 hpf embryos were observed morphologically. Figure 29 shows a representative morphant embryo. As indicated by the arrow, yolk sac edema was observed in 67% of the 48 morphants studied. Embryos observed at 56 hpf demonstrated normal morphology, a representative embryo is shown in Figure 30.

0154] Additional analyses were conducted on 48-56 hpf morphant embryos. A primary in situ hybridization screen with cdh5 on 14 morphants from the second dose group showed 79% as normal, the remaining 29% showing medium effects of reduced intersegmental expression. Microangiography on 29 first dose group morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 31. Of the 29 embryos, none had FITC-Dextran in the heart, 3% had FITC-Dextran

in the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 31. High effects were observed in 7% of the embryos, medium effects in 3% and low effects in 38%. No leaky vasculature was observed. Normal embryos accounted for 45% of the sample.

0155] GeneNOC8009C9

0156] The gene having the sequence shown in SEQ ID NO:38 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 32. Specific data are given below in Table 15. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:39) and the human homolog (SEQ ID NO:41) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 40 and 42, respectively.

0157] Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz241 and sz242, targeted to the zebrafish gene. Three (3)ng of sz241 morpholino and 1ng of sz242 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was

conducted.

0158] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe fli-1 revealed that 7% of the 15 morphant embryos assayed had medium effects. The probe flk-1 indicated that all 15 morphants observed were normal. The probe tie-1 indicated that 7% of the 15 morphants observed had high effects. The probe cdh5 indicated that 15% of the 20 morphants observed had low effects. Medium effects were seen in 5% and high effects in 15%. The probe flt-4 indicated that all 15 morphants observed were normal, and the probe tie-2 indicated that all 16 morphants observed were normal. Table 16 summarizes this data.

0159] At 28 hpf embryos were observed morphologically. Figure 33 shows a representative morphant embryo at 28 hpf. Mild cell death was observed in 25% of the 53 embryos observed. At 56 hpf 52 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 34. As indicated by the arrow, pericardial edema was seen in 13% of embryos. The arrowhead points toward a region of yolk sac edema, seen in 25% of embryos. Reduced IS blood flow was observed in 13% and 15% showed reduced axial blood flow.

160] Additional analyses were conducted on 48–56 hpf morphant embryos. A primary in situ hybridization screen with *cdh5* on 31 morphants showed all as normal. Microangiography on morphants was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 35. Of the 29 embryos, 7% had FITC–Dextran in the heart, and 14% in the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrows in Figure 35. High effects were observed in 3% of the embryos, medium effects in 3% and low effects in 21%. No leaky vasculature was observed. Normal embryos accounted for 52% of the sample. The data reveal that the gene is expressed in and around the heart and around organs, including some expression in select organs.

161] Gene NOC8009G23

162] The gene having the sequence shown in SEQ ID NO:43 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 36. Specific data are given below in Table 17. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:44) and the human homolog (SEQ ID NO:46) was also deduced. Proteins encoded by these sequences are given at SEQ ID

NO:s 45 and 47, respectively.

163] Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz149 and sz150, each targeted to the zebrafish gene. In a first dose group, 1.5ng of sz149 morpholino and 1.5ng of sz150 morpholino were administered to fertilized eggs. In a second dose group, 2ng of sz149 morpholino and 2ng of sz150 morpholino were administered to fertilized eggs. In a third dose group, 3ng of sz149 morpholino and 3ng of sz150 morpholino were administered to fertilized eggs. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

164] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In studies with embryos from the second dose group, the probe fli-1 revealed that 21% of the 14 morphant embryos assayed had high effects. The probe flk-1 indicated that all 16 morphants reviewed were normal. The probe tie-1 indicated that 36% of the 22 morphants observed had high effects. The probe cdh5 indicated that 13% of the 15 morphants observed had low effects with breaks in axial

expression. The probe flt-4 indicated that all 16 morphants observed were normal, and the probe tie-2 indicated that all 13 morphants observed were normal.

165] In studies from the second dose group, the probe fli-1 revealed that 13% of the 15 morphant embryos assayed had medium effects, 27% had high effects. The probe flk-1 indicated that 7% of the 15 morphants reviewed had low effects, 7% had medium effects and 20% had high effects. The probe tie-1 indicated that 62% of the 13 morphants observed had high effects. The probe cdh5 indicated that 25% of the 12 morphants observed had high effects, some with breaks in axial expression. The probe flt-4 indicated that 13% of the 15 morphants observed had low effects in the axial vessels, including breaks in axial expression and severely malformed tails. The probe tie-2 indicated that all 8 morphants observed were normal. Table 18 summarizes this data.

166] At 28 hpf embryos were observed morphologically. Figure 37 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, cell death was observed in 40% of the 20 embryos observed. As indicated by the arrowhead, yolk sac edema was observed in 55% of the morphants. Curly down body was seen in 40% of morphants. At 56 hpf

a total of 20 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 38. As shown by the arrow, pericardial edema was observed in 55% of morphants. The arrowhead points toward yolk sac edema, observed in 55% of morphants. Curly down body was reported in 30% of embryos.

0167] Additional analyses were conducted on 48–56 hpf morphant embryos. A primary in situ hybridization screen with *cdh5* on 22 morphants from the first dose group showed 90% as normal. Low effects of reduced intersegmental expression and curly down embryos were seen in 5% of the embryos, and high effects with very short tails were seen in 5% of embryos. A primary in situ hybridization screen with *cdh5* was also performed on 20 morphants from the third dose group, showing 80% as normal. Low effects of reduced intersegmental expression were seen in 5% of the embryos, and medium effects in 15% of embryos.

168] Microangiography on morphants was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 39. Of the 25 embryos, none had FITC–Dextran in the heart, or the heart and head. Reduced intersegmental vasculature was seen in 24% of the embryos

as indicated by the arrow in Figure 39. No leaky vasculature was observed. Normal embryos accounted for 76% of the sample, in example of normal intersegmental vessels is indicated by the arrowhead.

0169] Gene OJC8003C9

0170] The gene having the sequence shown in SEQ ID NO:48 was identified as selectively expressed in blood vessels based on microarray data, see Figure 40. Specific data are given below in Table 19. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:49) and the human homolog (SEQ ID NO:51) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 50 and 52, respectively.

0171] Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz129 and sz130, each targeted to the zebrafish gene. In a first dose group, 3ng of sz129 morpholino and 4.5ng of sz130 morpholino were administered to each fertilized egg. In a second dose group, 4ng of sz129 morpholino and 6ng of sz130 morpholino were administered to each fertilized egg. In a third dose group, 6ng of sz129 morpholino and 8ng of sz130 morpholino

were administered to each fertilized egg. In a fourth dose group, 6ng of sz129 morpholino and 9ng of sz130 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

172] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In embryos from the second dose group, the probe fli-1 revealed that 20% of the 10 morphant embryos assayed had low effects, 10% had medium effects and 10% had high effects. The probe flk-1 indicated that 11% of the 9 morphants reviewed had low effects, 33% had medium effects and 11% had high effects. The probe tie-1 indicated that 22% of the 9 morphants observed had high effects. The probe cdh5 indicated that 14% of the 7 morphants observed had medium effects and 14% had high effects. The probe flt-4 indicated that all 9 morphants observed were normal, and the probe tie-2 indicated that all 7 morphants observed were normal.

173] In embryos from the third dose group, the probe fli-1 revealed that 10% of the 10 morphant embryos assayed had medium effects, and 50% had high effects. The probe flk-

1 indicated that 25% of the 12 morphants reviewed had medium effects and 25% had high effects. The probe tie-1 indicated that 17% of the 6 morphants observed had low effects, and 50% had high effects. The probe cdh5 indicated that 40% of 5 morphants observed had medium effects. The probe flt-4 indicated that all 9 morphants observed were normal, and the probe tie-2 indicated that all 6 morphants observed were normal. Table 20 summarizes this data.

174] At 28 hpf embryos were observed morphologically. Figure 41 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, curly down body was found in 35% of the 20 morphants observed. At 56 hpf a total of 20 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 42. As indicated by the long arrow, 60% of the embryos had cell death with an associated expanded hindbrain ventricle. Yolk sac edema was observed in 25% of embryos, as indicated by the short arrow. The arrowhead points out the lack of pericardial edema associated with the yolk sac edema.

175] Additional analyses were conducted on 48-56 hpf morphant embryos. A primary in situ hybridization screen

with *cdh5* on 19 morphants from the first dose group showed all were normal. The primary in situ hybridization screen with *cdh5* on 10 morphants from the fourth dose group showed only 90% normal, the remaining 10% exhibiting low effects with curly tails. Microangiography on 19 morphants from the third dose group was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 43. Of the 19 embryos, none had FITC-Dextran in the heart and head but 16% had it in the heart alone. Reduced intersegmental vasculature was seen in 37% of the embryos. No leaky vasculature was observed. Normal embryos accounted for 47% of the sample.

176] Gene OJC8009J7

177] The gene having the sequence shown in SEQ ID NO:53 was identified as selectively expressed in blood vessels based on microarray data, see Figure 44. Specific data are given below in Table 21. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:54) and the human homolog (SEQ ID NO:56) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 55 and 57, respectively.

178] Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish

gene was identified for targeting. Two morpholinos were prepared, sz175 and sz176, each targeted to the zebrafish gene. Two (2) ng of sz175 morpholino and 12ng of sz176 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary in situ hybridization screen with six different probes was conducted.

179] Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe fli-1 revealed that 7% of the 14 morphant embryos assayed had low effects, and 29% had high effects. The probe flk-1 indicated that 25% of the 12 morphants reviewed had low effects and 8% had high effects. The probe tie-1 indicated that 11% of the 9 morphants observed had medium effects and 11% had high effects. The probe cdh5 indicated that 19% of the 16 morphants observed had low effects, 6% had medium effects, and 19% had high effects. The probe flt-4 indicated that all 10 morphants observed were normal, and the probe tie-2 indicated that all 6 morphants observed were normal. Table 22 summarizes this data.

180] At 28 hpf embryos were observed morphologically. Figure 45 shows a representative morphant embryo at 28 hpf. As

evidenced from the figure, particularly when viewed in light of the 28 hpf wild type embryo of Figure 4, the morphants exhibited normal morphology. At 56 hpf embryos again were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 46.

Again, the normal morphology observed in the embryos can be easily understood when Figure 46 is viewed in light of the 56 hpf wild type embryo of Figure 6.

181] Additional analyses were conducted on 48–56 hpf morphant embryos. A primary in situ hybridization screen with *cdh5* on 17 morphants showed 88% as normal. Medium effects of reduced intersegmental expression were seen in the other 12% of embryos. Microangiography on morphants was used to locate the presence of FITC–Dextran in various regions of the embryo, see Figure 47. Of the 33 embryos, none had FITC–Dextran in the heart and head combined, but 4% had it in the heart alone. Reduced intersegmental vasculature was seen in 15% of embryos. No leaky vasculature was observed. Normal embryos accounted for 81% of the sample. The leaks observed came from blood vessels in the posterior head as indicated by the arrowhead.

182] Novel Applications Ascertained from in vivo Data

183] The present invention relates to the eleven gene targets, and proteins related thereto, which were originally identified as upregulated during vasculogenesis or angiogenesis through microarray evaluation and subsequently proven to play a critical role in vivo with zebrafish embryo experimentation. These genes and proteins can form the basis of novel methods and treatments directed to angiogenesis-related conditions. For example, biological samples from a patient suspected of suffering from an angiogenesis-related condition can be screened to ascertain if genes or proteins of the present invention are expressed at the correct time, location, and intensity in the patient. Such screening methods form part of the claimed invention. If a gene and/or protein is identified as improperly expressed, therapies to correct the condition such as gene therapy or medicament can be initiated according to methods and procedures described herein or known in the art. With such specific data as is now possible using tools described herein, rapid diagnosis and specific, targeted treatment is possible.

184] One type of screening method envisioned relies on gene amplification for detecting patients with conditions related to vasculogenesis or angiogenesis. Such methods

could employ PCR, in situ hybridisation, and/or Southern blotting techniques to elucidate the condition. Another type of screening method could be based on evaluations of gene expression, using known techniques such as quantitative PCR, microarrays, Northern blotting, or in situ hybridisation. Yet another type of screening method that could be used would measure or monitor protein expression and could be effected with techniques such as immunohistochemistry, Western blotting, ELISA, or FACS.

185] If it is determined, through methods of the present invention or other methods, that an angiogenesis-related condition could be improved through administration of compounds containing genes and/or proteins according to the invention, one or more of the genes and/or proteins could be administered together or sequentially by methods known in the art.

186] Isolated nucleic acid molecules or proteins of the present invention can be obtained, for example, by synthesis using standard direct peptide synthesizing techniques or recombinant methods. Proteins may be isolated or purified in a variety of ways known to those skilled in the art, such as electrophoretic purification or chromatographic techniques.

- 187] Administration of the compounds of the present invention can be effected by any method that enables delivery of the compounds to the site of desired action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), and topical administration.
- 188] Gene therapy approaches may be used to introduce nucleotides of the present invention into a cell, group of cells, or organism. Both in vivo and ex vivo methods can be utilized. Vectors typically are used in this procedure. Non-virus or virus vectors could be employed, for example recombinant adenovirus or retrovirus. According to this use, the desired gene is introduced into a DNA virus or RNA virus, such as avirulent retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, poxvirus, poliovirus, Sindbis virus, Sendai virus, SV40, and immunodeficiency virus (HIV). The recombinant virus is then infected into the target cell(s). Multiple genes could be incorporated in a single vector, alternatively, they could be introduced to the target cell(s) in separate vectors simultaneously or sequentially. These methods are known in the art and are described in numerous patents and publications.

89] Another means to interfere with gene expression or protein production contemplated by the present invention is to employ small interfering RNA (siRNA). siRNA comprises a sense and antisense strand of RNA corresponding to the gene of interest, for example, SEQ ID NO:2. A siRNA molecule consists of approximately 19 nucleotides plus an overhang of approximately 2 nucleotides at the 3' end. Some preferred methods include between 19–23 nucleotides plus 3' overhang. The siRNA is introduced to the cell or cells of interest through known methods. Following introduction, the cell or cells destroy ssRNA having the same sequence. This results in a reduction or prevention in translation of a targeted gene and a corresponding reduction or prevention in protein production.

190] The amount of active compound administered can be determined after assessing the subject being treated, the severity of the disorder or condition, the rate of administration, and the disposition of the compound. Doses may be administered all at once, or spread out over a discrete time period.

191] Compounds of the present invention may be applied as a sole therapy or may involve one or more other active medicinal or pharmaceutical agent. Compositions may in-

clude carriers, adjuvants, buffers, or excipients as known in the art. If desired, the compositions may further contain ingredients such as flavorings, sweeteners, binders, dyes, lubricating agents, perfume, thickening agents, stabilizers, emulsifiers, dispersants, suspending agents, preservatives, and pH regulating agents. Compositions may be in any suitable form, for example, tablet, capsule, pill, powder, sustained release formulation, solution, suspension, emulsion, ointment or cream. The compositions may be sterile. Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known or apparent to those skilled in this art. The pharmaceutical compositions of the present invention that have been described can be applied to all diseases that require vasculogenic or angiogenic therapy. For example, one method for the treatment of an angiogenesis-related disorder involves a composition according to the present invention used to vascularize ischemic tissue. There are many ways to determine if a tissue is at risk of suffering ischemic damage from undesirable vascular occlusion. Such methods are well known in the art and include, for example, imaging techniques such as MRI to evaluate myocardial disease. After determining where and when to

apply compositions of the present invention, the compositions can be administered to increase angiogenesis in tissue affected by or at risk of being affected by a vascular occlusion. This could be an effective means of preventing and/or attenuating ischemia in such tissue. Methods are known in the art to evaluate and measure the degree to which ischemia has been attenuated.

[192] Further treatment methods according to the present invention include the use of any known technique that permits visualization, measurement, and/or evaluation of the functionality and degree of ischemia of the patient's heart. Such evaluations could be made prior to initiating treatment, during the course of treatment, after treatment has been completed, or at some or all stages. Examples of such techniques include echocardiography, cardiovascular nuclear imaging, magnetic resonance imaging, and contrast angiography.

[193] Although the present invention takes a step forward in the understanding of vasculogenesis and angiogenesis, and treatments for conditions related to the same, there is still a need in the art to further understand these conditions. Therefore, the present invention further contemplates the creation and use of non-human transgenic animals which

could be used for analysis and experimentation. Transgenic animals containing mutant, knock-out or modified genes corresponding to those disclosed herein are therefore also included in the invention. Transgenic animals are genetically modified animals into which recombinant, exogenous or cloned genetic material has been experimentally transferred. Such genetic material is often referred to as a transgene. The nucleic acid sequence of the transgene may be integrated either at a locus of a genome where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species than the species of the target animal.

- 194] Transgenic animals can be produced by a variety of different methods including transfection, electroporation, microinjection, gene targeting in embryonic stem cells and recombinant viral and retroviral infection as known in the art. The method of introduction of nucleic acid fragments into recombination competent mammalian cells can be by any method that favors co-transformation of multiple nucleic acid molecules. Detailed procedures for producing

transgenic animals are available to one skilled in the art, for example, U.S. Pat. Nos. 5,489,743 and 5,602,307.

95] Transgenic technology can be used to produce animals which lack one or more of the eleven genes described above. Such knockout animals can be used, especially when their growth and development is measured against data from a wild type or control animal, to elucidate timing and function of the deleted gene(s). Further, these animals could also be engineered to exhibit angiogenesis-related disease states, thus furthering the understanding of the role of the particular gene(s) in the progression of the selected disease. This knowledge would be an advance in the state of the art and could lead to promising new therapies for the prevention, management, and cure of disease.

196] Further uses of transgenic animals according to the present invention include replacement of one or more of the above-identified gene(s) in the research organism with the human homolog of the gene. For example, a transgenic mouse whose gene corresponding to SEQ ID NO:7 has been replaced with the human homolog, SEQ ID NO:9. While it is accepted that research into effective drug therapies can be conducted in animal models, such a trans-

genic mouse could be a more effective screening tool into potential drug candidates for human use.

197] SEQUENCE LISTING

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gaagtgtggaagagtgagcattattcatatgagctaaagcaagt-
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catctttttattgattgaatctttct

212] <210> 8 <211> 536 <212> PRT <213> Murinae gen.
sp.

213] Met Pro Gln Ser Pro Arg Ser Ala Pro Gly Leu Leu Leu Leu
Gln Ala Leu Val Ser Leu Val Ser Leu Ala Leu Val Ala Pro Ala
Arg Leu Gln Pro Ala Leu Trp Pro Phe Pro Arg Ser Val Gln
Met Phe Pro Arg Leu Leu Tyr Ile Ser Ala Glu Asp Phe Ser Ile
Asp His Ser Pro Asn Ser Thr Ala Gly Pro Ser Cys Ser Leu
Leu Gln Glu Ala Phe Arg Arg Tyr Tyr Asn Tyr Val Phe Gly
Phe Tyr Lys Arg His His Gly Pro Ala Arg Phe Arg Ala Glu
Pro Gln Leu Gln Lys Leu Leu Val Ser Ile Thr Leu Glu Ser Glu

Cys Glu Ser Phe Pro Ser Leu Ser Ser Asp Glu Thr Tyr Ser
Leu Leu Val Gln Glu Pro Val Ala Val Leu Lys Ala Asn Ser Val
Trp Gly Ala Leu Arg Gly Leu Glu Thr Phe Ser Gln Leu Val
Tyr Gln Asp Ser Phe Gly Thr Phe Thr Ile Asn Glu Ser Ser Ile
Ala Asp Ser Pro Arg Phe Pro His Arg Gly Ile Leu Ile Asp Thr
Ser Arg His Phe Leu Pro Val Lys Thr Ile Leu Lys Thr Leu Asp
Ala Met Ala Phe Asn Lys Phe Asn Val Leu His Trp His Ile Val
Asp Asp Gln Ser Phe Pro Tyr Gln Ser Thr Thr Phe Pro Glu
Leu Ser Asn Lys Gly Ser Tyr Ser Leu Ser His Val Tyr Thr Pro
Asn Asp Val Arg Met Val Leu Glu Tyr Ala Arg Leu Arg Gly
Ile Arg Val Ile Pro Glu Phe Asp Thr Pro Gly His Thr Gln Ser
Trp Gly Lys Gly Gln Lys Asn Leu Leu Thr Pro Cys Tyr Asn
Gln Lys Thr Lys Thr Gln Val Phe Gly Pro Val Asp Pro Thr Val
Asn Thr Thr Tyr Ala Phe Phe Asn Thr Phe Phe Lys Glu Ile
Ser Ser Val Phe Pro Asp Gln Phe Ile His Leu Gly Gly Asp Glu
Val Glu Phe Gln Cys Trp Ala Ser Asn Pro Asn Ile Gln Gly
Phe Met Lys Arg Lys Gly Phe Gly Ser Asp Phe Arg Arg Leu
Glu Ser Phe Tyr Ile Lys Lys Ile Leu Glu Ile Ile Ser Ser Leu Lys
Lys Asn Ser Ile Val Trp Gln Glu Val Phe Asp Asp Lys Val Glu
Leu Gln Pro Gly Thr Val Val Glu Val Trp Lys Ser Glu His Tyr
Ser Tyr Glu Leu Lys Gln Val Thr Gly Ser Gly Phe Pro Ala Ile
Leu Ser Ala Pro Trp Tyr Leu Asp Leu Ile Ser Tyr Gly Gln Asp
Trp Lys Asn Tyr Tyr Lys Val Glu Pro Leu Asn Phe Glu Gly

Ser Glu Lys Gln Lys Gln Leu Val Ile Gly Gly Glu Ala Cys Leu
Trp Gly Glu Phe Val Asp Ala Thr Asn Leu Thr Pro Arg Leu
Trp Pro Arg Ala Ser Ala Val Gly Glu Arg Leu Trp Ser Pro Lys
Thr Val Thr Asp Leu Glu Asn Ala Tyr Lys Arg Leu Ala Val
His Arg Cys Arg Met Val Ser Arg Gly Ile Ala Ala Gln Pro Leu
Tyr Thr Gly Tyr Cys Asn Tyr Glu Asn Lys Ile

214] <210> 9 <211> 1746 <212> DNA <213> Homo sapiens

215] ctgatccgggcccgggagggaagtcgggtcccgaggctccggctcggca-
gaccgggcggaagcagccgagcggccatggagctgtgctgggctggggct-
gccccggccgcccattgctgctggcgctgctgttggcgacactgctggcggc-
gatgttggcgctgctgactcaggtggcgctggtggtgcaggtggcggag-
gcggctcgggccccgagcgtctcggccaagccggggccggcgctgtggcc-
cctgccgctcttggtgaagatgaccccgaacctgctgcatctcgccccgga-
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gcatcatgaacctgctgaattccaggcctaaaac-
ccagggttcagcaacttctgtctcaatcacccttcagtcagagtgatgctttcc-
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tagccagttagtttatcaagattcttatggaactttcaccatcaatgaatccac-
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cattatctgccagttaagattattcttaaaactctggatgccatggcttt-
taataagtttaatgttcttcactggcacatagttgatgaccagtctttcccatatca-

gagcatcacttttcctgagttaagcaataaaggaagctattctttgtctcatgtt-
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gaattcgagtcctgccagaatttgatacccctgggcatacac-
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caaaacaagttggactcttttggacctataaaccctactctgaatacaacat-
acagcttccttactacatttttcaaagaaattagtgaggtgtttccagat-
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caatccaaaaattcaagatttcatgaggcaaaaaggctttggcacagattt-
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cataaacaagggatccattgtctggcaggagggttttgatgataaag-
caaagcttgcgccgggcacaatagttgaagtatggaaagacagcgcatatc-
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gagttccaaagatgtcagagatatggatgacgcctatgacagactgacaag-
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gatattgtaaccatgagaacatgtaa

216] <210> 10 <211> 556 <212> PRT <213> Homo sapiens

217] Met Glu Leu Cys Gly Leu Gly Leu Pro Arg Pro Pro Met Leu
Leu Ala Leu Leu Leu Ala Thr Leu Leu Ala Ala Met Leu Ala
Leu Leu Thr Gln Val Ala Leu Val Val Gln Val Ala Glu Ala Ala

Arg Ala Pro Ser Val Ser Ala Lys Pro Gly Pro Ala Leu Trp Pro
Leu Pro Leu Leu Val Lys Met Thr Pro Asn Leu Leu His Leu
Ala Pro Glu Asn Phe Tyr Ile Ser His Ser Pro Asn Ser Thr Ala
Gly Pro Ser Cys Thr Leu Leu Glu Glu Ala Phe Arg Arg Tyr
His Gly Tyr Ile Phe Gly Phe Tyr Lys Trp His His Glu Pro Ala
Glu Phe Gln Ala Lys Thr Gln Val Gln Gln Leu Leu Val Ser Ile
Thr Leu Gln Ser Glu Cys Asp Ala Phe Pro Asn Ile Ser Ser
Asp Glu Ser Tyr Thr Leu Leu Val Lys Glu Pro Val Ala Val Leu
Lys Ala Asn Arg Val Trp Gly Ala Leu Arg Gly Leu Glu Thr
Phe Ser Gln Leu Val Tyr Gln Asp Ser Tyr Gly Thr Phe Thr Ile
Asn Glu Ser Thr Ile Ile Asp Ser Pro Arg Phe Ser His Arg Gly
Ile Leu Ile Asp Thr Ser Arg His Tyr Leu Pro Val Lys Ile Ile
Leu Lys Thr Leu Asp Ala Met Ala Phe Asn Lys Phe Asn Val
Leu His Trp His Ile Val Asp Asp Gln Ser Phe Pro Tyr Gln Ser
Ile Thr Phe Pro Glu Leu Ser Asn Lys Gly Ser Tyr Ser Leu Ser
His Val Tyr Thr Pro Asn Asp Val Arg Met Val Ile Glu Tyr Ala
Arg Leu Arg Gly Ile Arg Val Leu Pro Glu Phe Asp Thr Pro
Gly His Thr Leu Ser Trp Gly Lys Gly Gln Lys Asp Leu Leu
Thr Pro Cys Tyr Ser Arg Gln Asn Lys Leu Asp Ser Phe Gly
Pro Ile Asn Pro Thr Leu Asn Thr Thr Tyr Ser Phe Leu Thr
Thr Phe Phe Lys Glu Ile Ser Glu Val Phe Pro Asp Gln Phe Ile
His Leu Gly Gly Asp Glu Val Glu Phe Lys Cys Trp Glu Ser
Asn Pro Lys Ile Gln Asp Phe Met Arg Gln Lys Gly Phe Gly

Thr Asp Phe Lys Lys Leu Glu Ser Phe Tyr Ile Gln Lys Val Leu
 Asp Ile Ile Ala Thr Ile Asn Lys Gly Ser Ile Val Trp Gln Glu
 Val Phe Asp Asp Lys Ala Lys Leu Ala Pro Gly Thr Ile Val Glu
 Val Trp Lys Asp Ser Ala Tyr Pro Glu Glu Leu Ser Arg Val Thr
 Ala Ser Gly Phe Pro Val Ile Leu Ser Ala Pro Trp Tyr Leu Asp
 Leu Ile Ser Tyr Gly Gln Asp Trp Arg Lys Tyr Tyr Lys Val Glu
 Pro Leu Asp Phe Gly Gly Thr Gln Lys Gln Lys Gln Leu Phe
 Ile Gly Gly Glu Ala Cys Leu Trp Gly Glu Tyr Val Asp Ala Thr
 Asn Leu Thr Pro Arg Leu Trp Pro Arg Ala Ser Ala Val Gly
 Glu Arg Leu Trp Ser Ser Lys Asp Val Arg Asp Met Asp Asp
 Ala Tyr Asp Arg Leu Thr Arg His Arg Cys Arg Met Val Glu
 Arg Gly Ile Ala Ala Gln Pro Leu Tyr Ala Gly Tyr Cys Asn His
 Glu Asn Met

218] <210> 11 <211> 676 <212> DNA <213> Murinae gen.
 sp. <221> misc_feature <222> (604)..(604) <223> n is
 a, c, g, or t

219] ggagctggtgggcccggagcggcggcgccgcatgtccgacagcga-
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 cacggcctgggaagaacgtgcagctgacagagaacgagatccgtggtctgt-
 gcctcaaatcccgggagattttcctgagccagcccattcttctggagcttgag-
 gcgcccctcaagatctgtggtgacatccatggccagtactatgaccttctacg-
 gctgtttgagtatggtggcttccctccagagagcaactac-
 ctcttcttgggggattatgtagatcggggcaagcagtccttggagaccatctgc-

ctgttgctggcctataagatcagatacccggagaatttcttc-
tacttcgtgggaaccatgagtggtgccagcatcaaccgcatttatggcttctat-
gatgaatgcaagagaagataacaacatcaaactgtggaagacgttcactgact-
gcttcaactgcctgcccattgcagccattgtggatgagaagatcttctgctgc-
cacggggggcctgtctccagacttgcaatccatggagcagattaggcggtattat-
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gaccctgacaagaaatagcctcca

220] <210> 12 <211> 1369 <212> DNA <213> Murinae gen.
sp.

221] ggaggcaggagagggcccggagctggtgggcccggagcggcggcgccgc-
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gaagtgcagggctcacggcctgggaagaacgtgcagctgacagagaacga-
gatccgtggtctgtgcctcaaatacccgggagattttcctgagccagcc-
cattcttctggagcttgaggcgcccctcaagatctgtggtgacatccatg-
gccagtactatgaccttctacggctgtttgagtatggtggcttccctccaga-
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tacttcgtgggaaccatgagtggtgccagcatcaaccgcatttatggcttctat-
gatgaatgcaagagaagataacaacatcaaactgtggaagacgttcactgact-
gcttcaactgcctgcccattgcagccattgtggatgagaagatcttctgctgc-
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gacagttggtgacactcttctcagctcccaactactgtggagagtttgacaat-
gctggtgccatgatgagtggtgatgagaccctcatgtgttccttccagatcct-
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cccggaggccggcccatcactccaccccgcaattctgccaaagccaa-
gaaatagcctccatgtgctgcccttctgccccagatcgtttgtacagaaatcat-
gctgccatgggtcacactggcctctcaggcccacccgtcacggggaaca-
cacagcgtaagtgtctttcctttatttttaagaatcaatagcagcatc-
taatctcccagggtccctcccaccagcacctgtggtggctgcaagtggaatc-
ctggggccaaggctgcagctcagggaatggcagacca-
gattgtgggtctccagccttgcattggctggcagccagatcctgggggcaacc-
catctgggtctcttgaataaagggtcaaagctggattctc

222] <210> 13 <211> 330 <212> PRT <213> Murinae gen.
sp.

223] Met Ser Asp Ser Glu Lys Leu Asn Leu Asp Ser Ile Ile Gly Arg
Leu Leu Glu Val Gln Gly Ser Arg Pro Gly Lys Asn Val Gln
Leu Thr Glu Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg
Glu Ile Phe Leu Ser Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro
Leu Lys Ile Cys Gly Asp Ile His Gly Gln Tyr Tyr Asp Leu Leu
Arg Leu Phe Glu Tyr Gly Gly Phe Pro Pro Glu Ser Asn Tyr
Leu Phe Leu Gly Asp Tyr Val Asp Arg Gly Lys Gln Ser Leu
Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile Arg Tyr Pro Glu

Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala Ser Ile
Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys
Leu Pro Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His
Gly Gly Leu Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg
Arg Ile Met Arg Pro Thr Asp Val Pro Asp Gln Gly Leu Leu
Cys Asp Leu Leu Trp Ser Asp Pro Asp Lys Asp Val Gln Gly
Trp Gly Glu Asn Asp Arg Gly Val Ser Phe Thr Phe Gly Ala
Glu Val Val Ala Lys Phe Leu His Lys His Asp Leu Asp Leu Ile
Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu Phe Phe
Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp
Glu Thr Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Asp
Lys Asn Lys Gly Lys Tyr Gly Gln Phe Ser Gly Leu Asn Pro
Gly Gly Arg Pro Ile Thr Pro Pro Arg Asn Ser Ala Lys Ala Lys
Lys

224] <210> 14 <211> 993 <212> DNA <213> Homo sapiens

225] atgtccgacagcgagaagctcaacctggactcgatcatcgggcgctgctg-
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gatccgcggtctgtgcctgaaatcccgggagatttttctgagccagcc-
cattcttctggagctggaggcaccctcaagatctgcggtgacatacacg-
gccagtactacgaccttctgcgactatttgagtatggcggtttccctcccga-
gagcaactacctctttctgggggactatgtggacaggggcaagcagtccttg-

gagaccatctgcctgctgctggcctataagatcaagtaccccgagaacttcttc-
ctgctccgtgggaaccacgagtggtgccagcatcaaccgcatctatggtttctac-
gatgagtgcaagagacgctacaacatcaaactgtggaaaaccttcactgact-
gcttcaactgcctgcccacgcggccatagtggacgaaaagatcttctgctgc-
cacggaggcctgtccccggacctgcagtgctatggagcagattcggcggat-
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gcgtctcttttacctttggagccgaggtggtggccaagttcctccacaagcac-
gacttgacctcatctgccgagcacaccaggtggtagaagacggctac-
gagttctttgccaagcggcagctggtgacacttttctcagctcccaactactgtg-
gcgagtttgacaatgctggcgccatgatgagtggtggacgagaccctcatgt-
gctctttccagatcctcaagcccgcgcgacaagaacaaggggaag-
tacggggcagttcagtggcctgaaccctggaggccgacccatcacccaccc-
cgcaattccgccaagccaagaaatag

226] <210> 15 <211> 330 <212> PRT <213> Homo sapiens

227] Met Ser Asp Ser Glu Lys Leu Asn Leu Asp Ser Ile Ile Gly Arg
Leu Leu Glu Val Gln Gly Ser Arg Pro Gly Lys Asn Val Gln
Leu Thr Glu Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg
Glu Ile Phe Leu Ser Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro
Leu Lys Ile Cys Gly Asp Ile His Gly Gln Tyr Tyr Asp Leu Leu
Arg Leu Phe Glu Tyr Gly Gly Phe Pro Pro Glu Ser Asn Tyr
Leu Phe Leu Gly Asp Tyr Val Asp Arg Gly Lys Gln Ser Leu
Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile Lys Tyr Pro Glu

Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala Ser Ile
Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys
Leu Pro Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His
Gly Gly Leu Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg
Arg Ile Met Arg Pro Thr Asp Val Pro Asp Gln Gly Leu Leu
Cys Asp Leu Leu Trp Ser Asp Pro Asp Lys Asp Val Gln Gly
Trp Gly Glu Asn Asp Arg Gly Val Ser Phe Thr Phe Gly Ala
Glu Val Val Ala Lys Phe Leu His Lys His Asp Leu Asp Leu Ile
Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu Phe Phe
Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp
Glu Thr Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Asp
Lys Asn Lys Gly Lys Tyr Gly Gln Phe Ser Gly Leu Asn Pro
Gly Gly Arg Pro Ile Thr Pro Pro Arg Asn Ser Ala Lys Ala Lys
Lys

228] <210> 16 <211> 702 <212> DNA <213> Murinae gen.
sp.

229] ggcatgacaggcagtgagcagggtgatgagccagggttggtgatctcttttagt-
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caacagcgtgaagtacccgtacatgacagtacatcccggtcccggtataactcgc-
catactggggcttggcttaccattttctctatgagtatggagaatctctgtct-
gtttactttaatgtcttgcattcgaattcctttgtcggcaatccctacatagccac-
cattacaaagccgtcggagccttttgttcggagtctcagctagtcagtc-
cttgactgacatcgctaagtataactataggcagtttgcgggccgcacttcttggc-
tatctgtaaccagactgggtcaaaaatcaactgcagtgatggctatattgag-
gactacatatgtcaaggggaatgaagagaaagtcaag-
gagggcagggtgtctttctactcgggacactcttcattctctatgtactgcatgct-
gtttgtcgcactttatcttcaagccaggatgaagggagactg

230] <210> 17 <211> 1432 <212> DNA <213> Murinae gen.
sp.

231] catccttagagctcgcccgccctgttggagaggggcacagggcagcg-
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gcgacagatcggcgggccactcgggtggcagggcgggccaatccaaactgcc-
ctgggtccctgctcccggtcagtctaagaggctcgcagtcgcttggggcgggccgc-
catcccgagggcggggctctgggaattgggtatctggaccgccgcggtct-
gttcctcccgccactcgcaccagggtggtgacaccatccagccggtgaccat-
gttcgacaagacgcggctgccgtacgtggccctcgatgtgatttgcgt-
gttgctggctggattgccttttgcaattcttacttcaaggcatacccccttccagc-
gaggaatatctgtaatgatgactccatcaagtacccttacaaggaagacac-
cataccttatgccttattaggtggaatagtcattccattctgtattatcgttatgag-
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gagtctcagctagtcagtccttgactgacatcgctaagtatactatag-
gcagtttgcgccgcacttcttggctatctgtaaccagactgggtcaaaaat-
caactgcagtgatggctatattgaggactacatatgtcaagggaatgaaga-
gaaagtcaaggagggcaggttgtctttctactcgggacactcttcattctctatg-
tactgcatgctgtttgtcgcactttatcttcaagccaggatgaaggga-
gactgggcaagactcttacgacccatgctccagtttgggctcattgctttttc-
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cacagttggactcattcagggagctgctatggctatactgggtgctttgtatg-
tatccgatttcttcaaggacacacattcttacaagagagaaaggaagag-
gatccacacacgactctccatgaaaccgccagttcacggaac-
tactgggcgctggcccgcttcaaaggcaacagctggagggctaaag-
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gctatctatacctcctggatgcccattttatgtgtgtacagttacttctaacaat-
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232] <210> 18 <211> 378 <212> PRT <213> Murinae gen.
sp.

233] Glu Ser Arg Arg Leu Arg Arg Gln Ile Gly Gly His Ser Val Ala
Gly Arg Pro Asn Pro Asn Cys Pro Gly Pro Cys Ser Arg Gln
Ser Lys Arg Leu Ala Val Ala Trp Gly Gly Arg His Pro Glu Gly
Gly Ala Leu Gly Ile Gly Tyr Leu Asp Arg Arg Gly Leu Phe
Leu Pro Pro Leu Ala Pro Gly Gly Asp Thr Ile Gln Pro Val Thr

Met Phe Asp Lys Thr Arg Leu Pro Tyr Val Ala Leu Asp Val
Ile Cys Val Leu Leu Ala Gly Leu Pro Phe Ala Ile Leu Thr Ser
Arg His Thr Pro Phe Gln Arg Gly Ile Phe Cys Asn Asp Asp
Ser Ile Lys Tyr Pro Tyr Lys Glu Asp Thr Ile Pro Tyr Ala Leu
Leu Gly Gly Ile Val Ile Pro Phe Cys Ile Ile Val Met Ser Ile Gly
Glu Ser Leu Ser Val Tyr Phe Asn Val Leu His Ser Asn Ser
Phe Val Gly Asn Pro Tyr Ile Ala Thr Ile Tyr Lys Ala Val Gly
Ala Phe Leu Phe Gly Val Ser Ala Ser Gln Ser Leu Thr Asp Ile
Ala Lys Tyr Thr Ile Gly Ser Leu Arg Pro His Phe Leu Ala Ile
Cys Asn Pro Asp Trp Ser Lys Ile Asn Cys Ser Asp Gly Tyr Ile
Glu Asp Tyr Ile Cys Gln Gly Asn Glu Glu Lys Val Lys Glu Gly
Arg Leu Ser Phe Tyr Ser Gly His Ser Ser Phe Ser Met Tyr
Cys Met Leu Phe Val Ala Leu Tyr Leu Gln Ala Arg Met Lys
Gly Asp Trp Ala Arg Leu Leu Arg Pro Met Leu Gln Phe Gly
Leu Ile Ala Phe Ser Ile Tyr Val Gly Leu Ser Arg Val Ser Asp
Tyr Lys His His Trp Ser Asp Val Thr Val Gly Leu Ile Gln Gly
Ala Ala Met Ala Ile Leu Val Ala Leu Tyr Val Ser Asp Phe Phe
Lys Asp Thr His Ser Tyr Lys Glu Arg Lys Glu Glu Asp Pro
His Thr Thr Leu His Glu Thr Ala Ser Ser Arg Asn Tyr Trp
Ala Leu Ala Arg Phe Lys Gly Asn Ser Trp Arg Leu Lys Ala
Gly Gly Cys Val Leu Leu Pro Ala Val Gln Thr Ile Leu

234] <210> 19 <211> 1626 <212> DNA <213> Homo sapi-
ens

35] tcagcgggaggggctggaccccgcggttcctcctccctgccgggtcccatcct-
taaagcgagagtctggacgccccgcctgtgggagagagcgccgggatccg-
gacggggagcaaccggggcaggccgtgccggctgaggagggtcctgaggc-
tacagagctgccgcggctggcacacgagcgccctcggcactaaccgagt-
gttcgcgggggctgtgaggggagggccccgggcgccattgctggcg-
gtgggagcgccgcccgggtctcagcccgccctcggctgctctcctcctccg-
gctgggaggggcccgtagctcggggccgtcgccagccccggcccgggctc-
gagaatcaagggcctcggccgcccgtcccgcagctcagtcctatcgcccttgc-
cgggcagccccgggcagagaccatgtttgacaagacgcggctgccgtacgtg-
gccctcgatgtgctctgcgtgttgctggcttccatgcctatggctgttc-
taaaattgggcaaataatatccatttcagagaggctttttctgtaaaga-
caacagcatcaactatccgtaccatgacagtaccgtcacatccactgtcctcatc-
ctagtggggggttggttgcccatttcctctattattcttggagaaaccctgtct-
gtttactgtaaccttttgactcaaattcctttatcaggaataactacatagccac-
tattacaaagccattggaacctttttatttggtgcagctgctagtccct-
gactgacattgccaagtattcaataggcagactgcggcctcacttcttggat-
gtttgtgatccagattggtcaaaaatcaactgcagcgatggttacattgaatac-
tacatatgtcgagggaatgcagaaagagttaaggaaggcagggtgtccttc-
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gcaatttggtcttggtgccgtatccatttatgtgggcctttctcgagtttctgat-
tataaacaccactggagcgatgtgttgactggactcattcaggggagctctg-
gttgcaatattagttgctgtatatgtatcggatttcttcaaagaaagaacttcttt-

taaagaaagaaaagaggaggactctcatacaactctgcatgaaacaccaa-
caactgggaatcactatccgagcaatcaccagccttgaaaggcagcaggggt-
gcccagggtgaagctggcctgttttctaaaggaaaatgattgccacaaggcaa-
gaggatgcatctttcttcctgggtgtacaagcctttaagacttctgctgctgctat-
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cacctgtatacatttttattaataaaaaaatgtaatgcttatgtataaacatgtatg-
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tatgggagaaccaa

236] <210> 20 <211> 378 <212> PRT <213> Homo sapiens

237] Gly Gly Pro Glu Ala Thr Glu Leu Pro Arg Leu Ala His Glu
Arg Leu Gly Thr Asn Arg Val Phe Ala Gly Ala Val Arg Gly
Gly Pro Arg Ala Pro Leu Leu Ala Val Gly Ala Pro Pro Gly Leu
Ser Pro Pro Ser Ala Ala Leu Leu Leu Arg Leu Gly Gly Ala Val
Ala Arg Gly Arg Arg Gln Pro Arg Pro Gly Leu Glu Asn Gln
Gly Pro Arg Pro Pro Ser Arg Ser Ser Val His Arg Pro Cys Arg
Ala Ala Arg Ala Glu Thr Met Phe Asp Lys Thr Arg Leu Pro
Tyr Val Ala Leu Asp Val Leu Cys Val Leu Leu Ala Ser Met
Pro Met Ala Val Leu Lys Leu Gly Gln Ile Tyr Pro Phe Gln Arg
Gly Phe Phe Cys Lys Asp Asn Ser Ile Asn Tyr Pro Tyr His
Asp Ser Thr Val Thr Ser Thr Val Leu Ile Leu Val Gly Val Gly
Leu Pro Ile Ser Ser Ile Ile Leu Gly Glu Thr Leu Ser Val Tyr
Cys Asn Leu Leu His Ser Asn Ser Phe Ile Arg Asn Asn Tyr

Ile Ala Thr Ile Tyr Lys Ala Ile Gly Thr Phe Leu Phe Gly Ala
Ala Ala Ser Gln Ser Leu Thr Asp Ile Ala Lys Tyr Ser Ile Gly
Arg Leu Arg Pro His Phe Leu Asp Val Cys Asp Pro Asp Trp
Ser Lys Ile Asn Cys Ser Asp Gly Tyr Ile Glu Tyr Tyr Ile Cys
Arg Gly Asn Ala Glu Arg Val Lys Glu Gly Arg Leu Ser Phe
Tyr Ser Gly His Ser Ser Phe Ser Met Tyr Cys Met Leu Phe
Val Ala Leu Tyr Leu Gln Ala Arg Met Lys Gly Asp Trp Ala
Arg Leu Leu Arg Pro Thr Leu Gln Phe Gly Leu Val Ala Val
Ser Ile Tyr Val Gly Leu Ser Arg Val Ser Asp Tyr Lys His His
Trp Ser Asp Val Leu Thr Gly Leu Ile Gln Gly Ala Leu Val Ala
Ile Leu Val Ala Val Tyr Val Ser Asp Phe Phe Lys Glu Arg Thr
Ser Phe Lys Glu Arg Lys Glu Glu Asp Ser His Thr Thr Leu
His Glu Thr Pro Thr Thr Gly Asn His Tyr Pro Ser Asn His
Gln Pro

238] <210> 21 <211> 816 <212> DNA <213> Homo sapiens

239] atttattcccttttgctagctggattgccttttgcaattcttacttcaaggcataccc-
cctccaacgaggagtattctgtaatgatgagtcctcatcaagtacccttacaaa-
gaagacaccataccttatgcggtattaggtggaataatcattccattcagtat-
tatcggtattattcttggagaaaccctgtctgtttactgtaaccttttgcact-
caaattcctttatcaggaataactacatagccactatttacaagccattggaac-
ctttttatttggtgcagctgctagtcagtcacctgactgacattgccaag-
tattcaataggcagactgcggcctcacttcttggatgtttgtgatccagattggt-
caaaaatcaactgcagcgatggttacattgaatactacatatgtcgagggaat-

gcagaaagagttaaggaaggcaggttgtccttctattcaggc-
cactcttcgttttccatgtactgcatgctgtttgtggcactt-
tatcttcaagccaggatgaagggagactgggcaagactcttacgccccacact-
gcaatttggtcttggtgccgtatccatttatgtgggcctttctcgagtttctgat-
tataaacaccactggagcgatgtgttgactggactcattcagggagctctg-
gttgcaatattagttgctgtatatgtatcggatttcttcaaagaaagaacttcttt-
taaagaaagaaaagaggaggactctcatacaactctgcatgaaacaccaa-
caactgggaatcactatccgagcaatcaccagccttga

240] <210> 22 <211> 271 <212> PRT <213> Homo sapiens

241] Ile Tyr Ser Leu Leu Leu Ala Gly Leu Pro Phe Ala Ile Leu Thr
Ser Arg His Thr Pro Phe Gln Arg Gly Val Phe Cys Asn Asp
Glu Ser Ile Lys Tyr Pro Tyr Lys Glu Asp Thr Ile Pro Tyr Ala
Leu Leu Gly Gly Ile Ile Ile Pro Phe Ser Ile Ile Val Ile Ile Leu
Gly Glu Thr Leu Ser Val Tyr Cys Asn Leu Leu His Ser Asn
Ser Phe Ile Arg Asn Asn Tyr Ile Ala Thr Ile Tyr Lys Ala Ile
Gly Thr Phe Leu Phe Gly Ala Ala Ala Ser Gln Ser Leu Thr
Asp Ile Ala Lys Tyr Ser Ile Gly Arg Leu Arg Pro His Phe Leu
Asp Val Cys Asp Pro Asp Trp Ser Lys Ile Asn Cys Ser Asp
Gly Tyr Ile Glu Tyr Tyr Ile Cys Arg Gly Asn Ala Glu Arg Val
Lys Glu Gly Arg Leu Ser Phe Tyr Ser Gly His Ser Ser Phe Ser
Met Tyr Cys Met Leu Phe Val Ala Leu Tyr Leu Gln Ala Arg
Met Lys Gly Asp Trp Ala Arg Leu Leu Arg Pro Thr Leu Gln
Phe Gly Leu Val Ala Val Ser Ile Tyr Val Gly Leu Ser Arg Val

Ser Asp Tyr Lys His His Trp Ser Asp Val Leu Thr Gly Leu Ile
Gln Gly Ala Leu Val Ala Ile Leu Val Ala Val Tyr Val Ser Asp
Phe Phe Lys Glu Arg Thr Ser Phe Lys Glu Arg Lys Glu Glu
Asp Ser His Thr Thr Leu His Glu Thr Pro Thr Thr Gly Asn
His Tyr Pro Ser Asn His Gln Pro

242] <210> 23 <211> 840 <212> DNA <213> Murinae gen.
sp. <221> misc_feature <222> (474)..(474) <223> n is
a, c, g, or t

243] ccgaagtaagtttgccagttttctgtcttatactgaggttcgccgggtcatggt-
gccagcctgactgagaagaggacgctcccgggaaacgaatgaggaaccac-
ctcctcctgctgttcaagtacagggggcctgggtgcgcaaagggaagaaaag-
caaaagacgaaaatggctaaatttaagatccgtccagccactgcctctgact-
gcagtgacatcctgcgactgatcaaggaactggctaaatatgaatacatggaa-
gatcaagtcattttaactgagaaagatctccaagaggatggctttggagaa-
cacccttctaccactgcctgggttgcaagaagtgccctaaagagcactggaccct-
gaaggacatagcattgttgggttcgccatgtactattttacctatgacccatg-
gattggcaagttgctgtatcttgaagacttcttcgtgatgagtgattacagag-
gctntgggtataggatcagaaattttgaagaatctaagccagggttgccatgaagt-
gtcgctgcagcagtatgcacttcttggttagcagaatggaatgaaccatctat-
caacttctacaaaagaagaggtgcttcggatctgtccagtga-
gagggatgggagggtcttcaagattgacaagagtacttgctaaaaatg-
gcagcagaggagtgaggcgtgccggtgtagaacatgacaacctccattgt-
gctttagaataattctcagcttcccttgctttctatcttgtgggtgtaggt-

gaaataatagagcgagccaccattccaaagctttattaccagtgacgtgttg-
catgtttgaaatcggtctggt

244] <210> 24 <211> 1052 <212> DNA <213> Murinae gen.
sp.

245] gctgcgagtttccccgaagtaagtttgccagttttctgtcttatactgag-
gttcgccgggtcatggtgccagcctgactgagaagaggacgctcc-
cgggaaacgaatgaggaaccacctcctcctgctgttcaagtacaggggcctg-
gtgcgcaaaggggaagaaaagcaaaagacgaaaatggctaaatttaagatc-
cgtccagccactgcctctgactgcagtgacatcctgcgactgatcaag-
gaactggctaaatatgaatacatggaagatcaagtcattttaactgagaaa-
gatctccaagaggatggctttggagaacacccccttctaccactgcctgggtgca-
gaagtgcctaaagagcactggaccctgaaggacatag-
cattgttgggttcgccatgtactattttacctatgacccatggattg-
gcaagttgctgtatcttgaagacttcttcgtgatgagtgattacagaggctttg-
gtataggatcagaaattttgaagaatctaagccagggttgccatgaagtgtcgct-
gcagcagtatgcacttcttggtagcagaatggaatgaaccatctatcaacttc-
tacaaaagaagagggtgcttcggatctgtccagtgaagagggatggag-
gctcttcaagattgacaaagagtacttgctaaaaatggcagcagaggagt-
gaggcgtgccggtgtagacaatgacaacctccattgtgcttta-
gaataattctcagcttcccttgctttctatcttgtgtgtagtgaaataatagagc-
gagcaccattccaaagctttattaccagtgacgttggtgcatgtttgaaattcg-
gtctgtttaaagtggcagtcatgtatgtggtttggaggcagaattcttgaa-
catcttttgatgaagaacaagggtggtatgatcttactatataagaaaaa-

caaaacttcattcttgtagtcatttaaattgtgtacaatgtacacactggtactta-
gagtttctgttttgattctttttttttaataaactactctttgattt

246] <210> 25 <211> 171 <212> PRT <213> Murinae gen.
sp.

247] Met Ala Lys Phe Lys Ile Arg Pro Ala Thr Ala Ser Asp Cys Ser
Asp Ile Leu Arg Leu Ile Lys Glu Leu Ala Lys Tyr Glu Tyr Met
Glu Asp Gln Val Ile Leu Thr Glu Lys Asp Leu Gln Glu Asp
Gly Phe Gly Glu His Pro Phe Tyr His Cys Leu Val Ala Glu Val
Pro Lys Glu His Trp Thr Pro Glu Gly His Ser Ile Val Gly Phe
Ala Met Tyr Tyr Phe Thr Tyr Asp Pro Trp Ile Gly Lys Leu
Leu Tyr Leu Glu Asp Phe Phe Val Met Ser Asp Tyr Arg Gly
Phe Gly Ile Gly Ser Glu Ile Leu Lys Asn Leu Ser Gln Val Ala
Met Lys Cys Arg Cys Ser Ser Met His Phe Leu Val Ala Glu
Trp Asn Glu Pro Ser Ile Asn Phe Tyr Lys Arg Arg Gly Ala Ser
Asp Leu Ser Ser Glu Glu Gly Trp Arg Leu Phe Lys Ile Asp
Lys Glu Tyr Leu Leu Lys Met Ala Ala Glu Glu

248] <210> 26 <211> 1111 <212> DNA <213> Homo sapi-
ens

249] gcgcagctcttagtcgcgggcccgcactggtgtttatccgtcactcgccgagggttc-
cttgggtcatggtgccagcctgactgagaagaggacgctcccgggagac-
gaatgaggaaccacctcctcctactgttcaagtacagggggcctggtccg-
caaagggaagaaaagcaaaagacgaaaatggctaaattcgtgatccgc-
ccagccactgccgcccgcactgcagtgacatactgcggctgatcaaggagctg-

gctaaatatgaatacatggaagaacaagtaatcttaactgaaaaagatctgcta-
gaagatgggttttggagagcacccttttaccactgcctgggtgcagaagtgcc-
gaaagagcactggactccggaaggtaaccctcgccctttccagaagccaga-
gagaccaacattgttgggttttggcatgtactattttacctatgaccctgtggattg-
gcaagttattgtatcttgaggacttcttcgtgatgagtgattatagagggtac-
gattgagctttggcataggatcagaaattctgaagaatctaagccagggttg-
caatgaggtgtcgtggcagcatgcacttcttgggcagaatggaatgaac-
catccatcaacttctataaaagaagagggtgcttctgatctgtccagtga-
gagggttggagactgttcaagatcgacaaggagtacttgctaaaaatg-
gcaacagaggagtgaggagtgtgctgctgtagatgacaacctccattctatttta-
gaataaattcccaacttctcttgctttctatgctgtttgtagtgaaataatagaat-
gagcaccattccaaagctttattaccagtggcggttggtgcatgtttgaaatgag-
gtctgtttaaagtggcaatctcagatgcagtttggagagtcagatctttctc-
cttgaatatctttcgataaacaacaagggtgggtgtgatct-
taatatatttgaaaaaaacttcattctcgtgagtcatttaaattgtgtacaatgtaca-
cactgggtacttagagtttctgtttgattcttttttaataaaactactctttgatttaattc-
taaaaaaaaaaaaaaaaaaagaca

250] <210> 27 <211> 190 <212> PRT <213> Homo sapiens

251] Glu Pro Pro Pro Pro Thr Val Gln Val Gln Gly Pro Gly Pro Gln
Arg Glu Glu Lys Gln Lys Thr Lys Met Ala Lys Phe Val Ile Arg
Pro Ala Thr Ala Ala Asp Cys Ser Asp Ile Leu Arg Leu Ile Lys
Glu Leu Ala Lys Tyr Glu Tyr Met Glu Glu Gln Val Ile Leu Thr
Glu Lys Asp Leu Leu Glu Asp Gly Phe Gly Glu His Pro Phe

Tyr His Cys Leu Val Ala Glu Val Pro Lys Glu His Trp Thr Pro
Glu Gly Asn Pro Ser Pro Phe Pro Glu Ala Arg Glu Thr Asn Ile
Val Gly Phe Ala Met Tyr Tyr Phe Thr Tyr Asp Pro Trp Ile Gly
Lys Leu Leu Tyr Leu Glu Asp Phe Phe Val Met Ser Asp Tyr
Arg Gly Thr Ile Glu Leu Trp His Arg Ile Arg Asn Ser Glu Glu
Ser Lys Pro Gly Cys Asn Glu Val Ser Leu Ala Ala Cys Thr Ser
Trp Ala Glu Trp Asn Glu Pro Ser Ile Asn Phe Tyr Lys Arg
Arg Gly Ala Ser Asp Leu Ser Ser Glu Glu Gly Trp Arg

252] <210> 28 <211> 745 <212> DNA <213> Murinae gen.
sp.

253] aatctatggagcagattcggcgaattatgagaccaactgatgtaccagat-
caaggtcttctttgtgatctttggtggtctgaccccgatgaaagatgtcttag-
gctggggtgaaaatgacagaggagtgtccttcacatttggtgcagaagtg-
gttgcaaaatttctccataagcatgattcggatcttatatgtagagcc-
catcaggtggttgaagatggctatgagtttttcgcaaagaggcagttagt-
cactctgttggtctgagagcccaactactgtggcgagtttgacaatgcaggcgc-
catgatgagtgtggatgagaccctcatgtgttccttcagattttaagcctgca-
gagaaaaagaagcccaacgccacgagacctgtcacaccaccacgggggtat-
gatcacaagcaagcaaagaaatagatgtcacttgacactgcctg-
gttgggacttgtaacatagcggttcataaccttccttttaactgtgatgtgctg-
gtcagcttgcccaggtagacctgtctgtcgggccctcctccatttgattact-
gctggcacttgctgggttatagcagcaagccaagcacttcattctcaagagag-
catttggttctgaacctctgttccctttgtggacagctctgatgatgggtgt-

taagctgtacaccctggcagggttatcctgtctgaggagaaagtgtgta-
caattgatcttttttagtttagtataagtcattg

254] <210> 29 <211> 2127 <212> DNA <213> Murinae gen.
sp.

255] gctgctgcgggaggggtcggcggcgggacggcgatggcggatatcga-
caaactcaacatcgacagcatcatccaacggctgctggaagtgagaggggtc-
caagccaggcaagaatgtccagctccaggagaacgagatccgaggactct-
gcctgaagtctcgggagatcttcctcagtcagcctatccttttagaacttgaag-
caccactcaagatatgtggtgacatccacgggacagtactatgatttgctccgtct-
gtttgaatacgggtggctttcctccagagagcaactatttgtttctcggggactat-
gtggacaggggcaagcagtccttgagacaatctgcctcttgctggccta-
caaatcaagtatccggagaacttctttcttctcagaggggaaccacgagt-
gcgccagcatcaataggatctacggattttatgatgagtgtaaaagaagata-
caacattaagctgtggaaaacggtcacagactgttttaactgcttgcc-
gatagcagccatcgtggacgagaagatattctgctgtcatggagggtttat-
caccagatcttcaatctatggagcagattcggcgaattatgagaccaactgatg-
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cactctgttttctgcaccaactactgtggcgagtttgacaatgcaggcgccat-
gatgagtgtggatgagaccctcatgtgttccttcagattttaagcctgcaga-
gaaaaagaagcccaacgccacgagacctgtcacaccaccacgggggtatgat-

cacaaagcaagcaaagaaatagatgtcacttgacactgcctgggtgggacttg-
taacatagcgttcataaccttcctttttaactgtgatgtgctggtcagcttgc-
ccaggtagacctgtctgtcgggccctcctccatttgattactgctg-
gcacttgctgggttatagcagcaagccaagcacttcattctcaagagag-
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gagccttagagtgcgtgagtcctctacatgtaattgtcataaatgcattctgttgat-
acaaccactgtgaacaatttttttccagtttgtttgaaagggactgctttccct-
cattgtcttgtcatgtacaaactagtgtctgcagctgtggcagcaggagtgc-
ctgcctgccgccagccctgccagactatctgaagcacactccttcccactgca-
catttaataatgattaaagccattcttttcaatgtctgtgattccttcctaaagc-
caaagtttctgttggactgtatggcacgccctgggggatgaggtg-
gccagggcatcgaggctgcgtgcacaggccgcctccctccgtgggggcctca-
gaagcaggttattttaactagcaatagtgggtatagtgcgtgagtaagctattaat-
gatggaagttaatgacactttgtacagttcccatatagtctattcactgagt-
gatctttttacagttggatcaggcctgaacccgtccattcagaaagcttcaaat-
tatagaaacaacactgtcctatacgagtgaccgataatgctttctttggcta-
cattctttattctgcggtgacattgaggcttataaatcaaaaggaactaacttgc-
cgtccaccgggtttatacagaactcacagtatctatgacttttttaactacgacct-
gttaaataaatctgtttgcacagatgcccggtgtacaatgccatgtgctga-
gaatgggttcagacttattaaatgcaagcttggt

256] <210> 30 <211> 323 <212> PRT <213> Murinae gen.

sp.

[257] Met Ala Asp Ile Asp Lys Leu Asn Ile Asp Ser Ile Ile Gln Arg
Leu Leu Glu Val Arg Gly Ser Lys Pro Gly Lys Asn Val Gln
Leu Gln Glu Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg
Glu Ile Phe Leu Ser Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro
Leu Lys Ile Cys Gly Asp Ile His Gly Gln Tyr Tyr Asp Leu Leu
Arg Leu Phe Glu Tyr Gly Gly Phe Pro Pro Glu Ser Asn Tyr
Leu Phe Leu Gly Asp Tyr Val Asp Arg Gly Lys Gln Ser Leu
Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile Lys Tyr Pro Glu
Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala Ser Ile
Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys
Leu Pro Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His
Gly Gly Leu Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg
Arg Ile Met Arg Pro Thr Asp Val Pro Asp Gln Gly Leu Leu
Cys Asp Leu Leu Trp Ser Asp Pro Asp Lys Asp Val Leu Gly
Trp Gly Glu Asn Asp Arg Gly Val Ser Phe Thr Phe Gly Ala
Glu Val Val Ala Lys Phe Leu His Lys His Asp Leu Asp Leu Ile
Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu Phe Phe
Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp
Glu Thr Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Glu Lys
Lys Lys Pro Asn Ala Thr Arg Pro Val Thr Pro Pro Arg Gly

Met Ile Thr Lys Gln Ala Lys Lys

258] <210> 31 <211> 993 <212> DNA <213> Homo sapiens
atgt

259] ccgacagcgagaagctcaacctggactcgatcatcgggcgctgctggaagt-
gcagggctcgcggcctggcaagaatgtacagctgacagagaacgagatc-
cgcggtctgtgcctgaaatcccgggagattttctgagccagcccattcttctg-
gagctggaggcaccctcaagatctgcggtgacatacacggccagtactac-
gaccttctgcgactatttgagtatggcggtttccctcccgagagcaactac-
ctctttctgggggactatgtggacaggggcaagcagtccttgagaccatct-
gcctgctgctggcctataagatcaagtaccccgagaacttcttcctgctc-
cgtgggaaccacgagtggtgccagcatcaaccgcatctatggtttctacgat-
gagtgaagagacgctacaacatcaaactgtggaaaaccttcactgact-
gcttcaactgcctgcccacgcggccatagtggacgaaaagatcttctgctgc-
cacggaggcctgtccccggacctgcagtctatggagcagattcggcggat-
catgcggcccacagatgtgcctgaccagggcctgctgtgtgacctgctgtg-
gtctgaccctgacaaggacgtgcagggctggggcgagaacgaccgtg-
gcgtctcttttacctttggagccgagggtggtggccaagttcctccacaagcac-
gacttggacctcatctgccgagcacaccagggtggtagaagacggctac-
gagttctttgccaagcggcagctggtgacacttttctcagctcccaactactgtg-
gcgagtttgacaatgctggcgccatgatgagtggtggacgagaccctcatgt-
gctctttccagatcctcaagcccggcgacaagaacaagggggaag-
tacgggagcagttcagtggcctgaaccctggaggccgacccatcacccaccc-
cgcaattccgccaagccaagaaatag

260] <210> 32 <211> 330 <212> PRT <213> Homo sapiens

261] Met Ser Asp Ser Glu Lys Leu Asn Leu Asp Ser Ile Ile Gly Arg
Leu Leu Glu Val Gln Gly Ser Arg Pro Gly Lys Asn Val Gln
Leu Thr Glu Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg
Glu Ile Phe Leu Ser Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro
Leu Lys Ile Cys Gly Asp Ile His Gly Gln Tyr Tyr Asp Leu Leu
Arg Leu Phe Glu Tyr Gly Gly Phe Pro Pro Glu Ser Asn Tyr
Leu Phe Leu Gly Asp Tyr Val Asp Arg Gly Lys Gln Ser Leu
Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile Lys Tyr Pro Glu
Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala Ser Ile
Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys
Leu Pro Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His
Gly Gly Leu Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg
Arg Ile Met Arg Pro Thr Asp Val Pro Asp Gln Gly Leu Leu
Cys Asp Leu Leu Trp Ser Asp Pro Asp Lys Asp Val Gln Gly
Trp Gly Glu Asn Asp Arg Gly Val Ser Phe Thr Phe Gly Ala
Glu Val Val Ala Lys Phe Leu His Lys His Asp Leu Asp Leu Ile
Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu Phe Phe
Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp
Glu Thr Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Asp
Lys Asn Lys Gly Lys Tyr Gly Gln Phe Ser Gly Leu Asn Pro

Gly Gly Arg Pro Ile Thr Pro Pro Arg Asn Ser Ala Lys Ala Lys
Lys

262] <210> 33 <211> 747 <212> DNA <213> Murinae gen.
sp. <221> misc_feature <222> (298)..(298) <223> n is
a, c, g, or t

263] cgacaagtcattgctgctcgctatgaataagggtgaaggagacaacattagcg-
gcgtttgcttcgttggcctgtatgacctggacgcctctcgctacttcgtccttct-
gcctctgtgcctctgcgtatttggtgagctgggagagtagcccagtg-
gtacagcgcccacctggaatacttgaggacctgggggtgtctcccagcactg-
caaaaggaaaattcactgttacagtcttccttgacttaaacagctttgtc-
tattgttttttggtttggccttggtactttgttgctgnt-
tattttgttggtgttggtttgttggttgagacaggggtttttgttagccctgact-
gtcctgaaactccctctgtagaccaggctggcctcaaacttacagagatccgc-
ctgcctcagcctccaagtgtggaataatggtgtggtcaccaccgcccagc-
ctttgtctatttttaaaacttgaaagaaacaacagccca-
gatttcaaaaataataatgcacttatacctaaaaaaacaaccaggagtgc-
ccagttaataacatttttaaatgtggggatgggaagggcattagag-
gagtcttccttctattgaagattcattaaagtatttaagatatgccctttcactctt-
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tagatatgaatttgaaaatatgcttatgtgta

264] <210> 34 <211> 2021 <212> DNA <213> Murinae gen.
sp.

265] gggcaagaaacttcaacagaagtccacacctccccagaagcatccgtcaaa-

gagggacgagcagaccgagcaaactcccagcgccaaagatcgggact-
gtggggaatctgcagggcccagttccaagctctctgggaaccggaacg-
gcaggggaaagccgagcgggcggcctgaaggagagaagcaatggatca-
gagggggctccaagtgaaggaagggtaagtccaaagagcagcgcttcctga-
gactggcctgatagactgcagcacttcacaggccgccagttctccagaac-
caaccagcctcaagggctccacatctctgcctgttcactcagcttcagagc-
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caaaaggaaaattcactgttacagtcttccttgcaactaaaccagctttgtc-
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caccactgcccagccttttgctgttttttaaacttgaaagaaacaacagccca-
gatttcaaaaataataatgcatttatacctaaaaaaccaaccaggagtgc-
ccagttaataacactttttaaatgtggggatggggaagggcattagag-
gagtcttccttctattgaagattcattaaagtattttaagatatgctctttcactctt-
tatataaatccaagatttttctttgctgaagtatttaaaacttttgtagcttttatatg-
tagatatgaatttgaaaatatgcttatgtgtatttgaacttttgaaaatcctaga-
gaattgaatcaaataatttttatgatgtttttctactatttagctactttgcgactgt-
gatagctgttacactggatttttaaaaaacttgtagcagcctctt-

tacagtaaaaagagtgggtgtcacactgaaagggtctgtaagaagtgggt-
cacagccaccccctaccttccccaaaaggaggaacttggtggcagggtccctcc-
ctgattggactgtccctttctttctgcatgttataaatcagcaggtaagatggtag-
gtttttacaagttaggccgagctgtcgattccccttttaagtgttgaattag-
gattgaattatggccatttgtagttgctcgtgcctgtctttatttttagtattttatttc-
ccgagacaggaactcactgtgtgggtgctccttggtgtctggtgttcagtct-
gtcccaggcaggtcacagagatctccccctctgcagcccactcatctctcc-
caagccaccacactcagcttttatctgttttaaaaatttaaaacttaaaaaaat-
gtttttggaatagtacaaacacattgtgttgtaaatttctttgatgctatg-
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gagtcagagttgggcaggaagagtgtagtgcagcagatgcagcgtgaaga-
cactgaagggtgctaagacagcgtctcagtgtctgggtcctccttaaggat-
tatctcgccagcgagggttttcttagatactttgatcccattggagctctgt-
taaagtttaaaatgaaaattatcatgtactgtatgggaaatgtaaatac-
taacttttccacatatgtaaacttcagacacaaattttttgtgtgttctttcat-
caataaaattttctttgtat

266] <210> 35 <211> 709 <212> PRT <213> Murinae gen.
sp.

267] Met Glu Arg Ser Pro Phe Leu Leu Ala Cys Ile Leu Leu Pro
Leu Val Arg Gly His Ser Leu Phe Thr Cys Glu Pro Ile Thr Val
Pro Arg Cys Met Lys Met Thr Tyr Asn Met Thr Phe Phe Pro
Asn Leu Met Gly His Tyr Asp Gln Gly Ile Ala Ala Val Glu Met
Gly His Phe Leu His Leu Ala Asn Leu Glu Cys Ser Pro Asn

Ile Glu Met Phe Leu Cys Gln Ala Phe Ile Pro Thr Cys Thr Glu
Gln Ile His Val Val Leu Pro Cys Arg Lys Leu Cys Glu Lys Ile
Val Ser Asp Cys Lys Lys Leu Met Asp Thr Phe Gly Ile Arg
Trp Pro Glu Glu Leu Glu Cys Asn Arg Leu Pro His Cys Asp
Asp Thr Val Pro Val Thr Ser His Pro His Thr Glu Leu Ser Gly
Pro Gln Lys Lys Ser Asp Gln Val Pro Arg Asp Ile Gly Phe Trp
Cys Pro Lys His Leu Arg Thr Ser Gly Asp Gln Gly Tyr Arg
Phe Leu Gly Ile Glu Gln Cys Ala Pro Pro Cys Pro Asn Met
Tyr Phe Lys Ser Asp Glu Leu Asp Phe Ala Lys Ser Phe Ile Gly
Ile Val Ser Ile Phe Cys Leu Cys Ala Thr Leu Phe Thr Phe Leu
Thr Phe Leu Ile Asp Val Arg Arg Phe Arg Tyr Pro Glu Arg
Pro Ile Ile Tyr Tyr Ser Val Cys Tyr Ser Ile Val Ser Leu Met
Tyr Phe Val Gly Phe Leu Leu Gly Asn Ser Thr Ala Cys Asn
Lys Ala Asp Glu Lys Leu Glu Leu Gly Asp Thr Val Val Leu
Gly Ser Lys Asn Lys Ala Cys Ser Val Val Phe Met Phe Leu
Tyr Phe Phe Thr Met Ala Gly Thr Val Trp Trp Val Ile Leu Thr
Ile Thr Trp Phe Leu Ala Ala Gly Arg Lys Trp Ser Cys Glu Ala
Ile Glu Gln Lys Ala Val Trp Phe His Ala Val Ala Trp Gly Ala
Pro Gly Phe Leu Thr Val Met Leu Leu Ala Met Asn Lys Val
Glu Gly Asp Asn Ile Ser Gly Val Cys Phe Val Gly Leu Tyr Asp
Leu Asp Ala Ser Arg Tyr Phe Val Leu Leu Pro Leu Cys Leu
Cys Val Phe Val Gly Leu Ser Leu Leu Leu Ala Gly Ile Ile Ser
Leu Asn His Val Arg Gln Val Ile Gln His Asp Gly Arg Asn

Gln Glu Lys Leu Lys Lys Phe Met Ile Arg Ile Gly Val Phe Ser
Gly Leu Tyr Leu Val Pro Leu Val Thr Leu Leu Gly Cys Tyr
Val Tyr Glu Leu Val Asn Arg Ile Thr Trp Glu Met Thr Trp
Phe Ser Asp His Cys His Gln Tyr Arg Ile Pro Cys Pro Tyr Gln
Ala Asn Pro Lys Ala Arg Pro Glu Leu Ala Leu Phe Met Ile
Lys Tyr Leu Met Thr Leu Ile Val Gly Ile Ser Ala Val Phe Trp
Val Gly Ser Lys Lys Thr Cys Thr Glu Trp Ala Gly Phe Phe Lys
Arg Asn Arg Lys Arg Asp Pro Ile Ser Glu Ser Arg Arg Val
Leu Gln Glu Ser Cys Glu Phe Phe Leu Lys His Asn Ser Lys
Val Lys His Lys Lys Lys His Gly Ala Pro Gly Pro His Arg Leu
Lys Val Ile Ser Lys Ser Met Gly Thr Ser Thr Gly Ala Thr Thr
Asn His Gly Thr Ser Ala Met Ala Ile Ala Asp His Asp Tyr Leu
Gly Gln Glu Thr Ser Thr Glu Val His Thr Ser Pro Glu Ala Ser
Val Lys Glu Gly Arg Ala Asp Arg Ala Asn Thr Pro Ser Ala
Lys Asp Arg Asp Cys Gly Glu Ser Ala Gly Pro Ser Ser Lys
Leu Ser Gly Asn Arg Asn Gly Arg Glu Ser Arg Ala Gly Gly
Leu Lys Glu Arg Ser Asn Gly Ser Glu Gly Ala Pro Ser Glu Gly
Arg Val Ser Pro Lys Ser Ser Val Pro Glu Thr Gly Leu Ile Asp
Cys Ser Thr Ser Gln Ala Ala Ser Ser Pro Glu Pro Thr Ser Leu
Lys Gly Ser Thr Ser Leu Pro Val His Ser Ala Ser Arg Ala Arg
Lys Glu Gln Gly Ala Gly Ser His Ser Asp Ala

268] <210> 36 <211> 2039 <212> DNA <213> Homo sapi-
ens

69] aggagacaacattagtggagtttgcttggcctttatgacctggat-
gcttctcgctactttgtactcttgccactgtgcctttgtgt-
gtttgttgggctctctcttcttttagctggcattatttccttaaatacatgttcga-
caagtcatacaacatgatggccggaaccaagaaaaactaaagaatttat-
gattcgaattggagcttccagcggcttgatcttgtgccattagtgcacttctcg-
gatgttacgtctatgagcaagtgaacaggattacctggga-
gataacttgggtctctgatcattgtcgtcagtagccatcccatgtcct-
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ctgatgacattaattgttggcatctctgctgtcttctgggttggaagcaaaaaga-
catgcacagaatgggctgggttttttaaacgaaatcgcaagagagatc-
caatcagtgaaagtcgaagagtactacaggaatcatgtgagtttttcttaaag-
cacaattctaaagttaaacacaaaaagaagcactataaaccaagttcaca-
caagctgaaggctcatttccaaatccatgggaaccagcacaggagc-
tacagcaaatacatggcacttctgcagtagcaattactagccatgattacctag-
gacaagaaactttgacagaaatccaaacctcaccagaaacatcaatgaga-
gaggtgaaagcggacggagctagcacccccagggttaagagaaacaggact-
gtggtgaacctgcctcgccagcagcatccatctcca-
gactctctgggggaacagggtcgacgggaagggccaggcaggcagtgatatct-
gaaagtgcgcggagtgaaggaaggattagttcaaagagtgatattactga-
cactggcctggcacagagcaacaatttgcagggtccccagttcttcagaac-
caagcagcctcaaagggttccacatctctgcttgttcaccgggttcaggagtga-
gaaaagagcagggaggtggtgtcattcagatacttgaagaa-
cattttctctcgttactcagaagcaaatttgtgttacactggaagtgcctatg-

cactgttttgtaagaatcactgttacattcttcttttgacttaaagttgcattgcc-
tactgttatactggaaaaaatagagttcaagaataatatgactcatttcaca-
caaaggttaatgacaacaatatacctgaaaacagaaaatgtgcaggt-
taataatattttttaatagtgtgggaggacagagtttagaggaatcttcctttc-
tatttatgaagattctactcttggttaagagtattttaagatgtactatgctattt-
tacttttttgatataaaatcaagatatttctttgctgaagtatttaaactttatccttg-
tatctttttatacatatttgaaaataagcttatatgtatttgaactttttgaaatcc-
tattcaagtatttttatcatgctattgtgatatttttagcactttggttagcttttacact-
gaatttctaagaaaattgtaaaatagtcttcttttatactgtaaaaaaagatatatac-
caaaaagtcttataataggaatttaacttttaaaaaccacttattgataccttac-
catctaaaatgtgtgatttttatagtctcgtttttaggaatttcacagatctaaattat-
gtaactgaaataagggtgcttactcaaagagtggtccactattgattgtattatgct-
gctcactgatccttctgcatatttaaaataaaaatgtcctaaaggggttagtaga-
caaatgttagtcttttgatatattaggccaagtgcattgacttccctttttaat-
gtttcatgaccaccattgattgtattataaccacttacagttgct-
tatattttttgttttaacttttgtttttaacatttagaatattacattttgtattat-
acagtacctttctcagacattttgtag

270] <210> 37 <211> 706 <212> PRT <213> Homo sapiens

271] Met Glu Met Phe Thr Phe Leu Leu Thr Cys Ile Phe Leu Pro
Leu Leu Arg Gly His Ser Leu Phe Thr Cys Glu Pro Ile Thr Val
Pro Arg Cys Met Lys Met Ala Tyr Asn Met Thr Phe Phe Pro
Asn Leu Met Gly His Tyr Asp Gln Ser Ile Ala Ala Val Glu Met
Glu His Phe Leu Pro Leu Ala Asn Leu Glu Cys Ser Pro Asn

Ile Glu Thr Phe Leu Cys Lys Ala Phe Val Pro Thr Cys Ile Glu
Gln Ile His Val Val Pro Pro Cys Arg Lys Leu Cys Glu Lys Val
Tyr Ser Asp Cys Lys Lys Leu Ile Asp Thr Phe Gly Ile Arg Trp
Pro Glu Glu Leu Glu Cys Asp Arg Leu Gln Tyr Cys Asp Glu
Thr Val Pro Val Thr Phe Asp Pro His Thr Glu Phe Leu Gly
Pro Gln Lys Lys Thr Glu Gln Val Gln Arg Asp Ile Gly Phe Trp
Cys Pro Arg His Leu Lys Thr Ser Gly Gly Gln Gly Tyr Lys Phe
Leu Gly Ile Asp Gln Cys Ala Pro Pro Cys Pro Asn Met Tyr
Phe Lys Ser Asp Glu Leu Glu Phe Ala Lys Ser Phe Ile Gly Thr
Val Ser Ile Phe Cys Leu Cys Ala Thr Leu Phe Thr Phe Leu
Thr Phe Leu Ile Asp Val Arg Arg Phe Arg Tyr Pro Glu Arg
Pro Ile Ile Tyr Tyr Ser Val Cys Tyr Ser Ile Val Ser Leu Met
Tyr Phe Ile Gly Phe Leu Leu Gly Asp Ser Thr Ala Cys Asn
Lys Ala Asp Glu Lys Leu Glu Leu Gly Asp Thr Val Val Leu
Gly Ser Gln Asn Lys Ala Cys Thr Val Leu Phe Met Leu Leu
Tyr Phe Phe Thr Met Ala Gly Thr Val Trp Trp Val Ile Leu Thr
Ile Thr Trp Phe Leu Ala Ala Gly Arg Lys Trp Ser Cys Glu Ala
Ile Glu Gln Lys Ala Val Trp Phe His Ala Val Ala Trp Gly Thr
Pro Gly Phe Leu Thr Val Met Leu Leu Ala Met Asn Lys Val
Glu Gly Asp Asn Ile Ser Gly Val Cys Phe Val Gly Leu Tyr Asp
Leu Asp Ala Ser Arg Tyr Phe Val Leu Leu Pro Leu Cys Leu
Cys Val Phe Val Gly Leu Ser Leu Leu Leu Ala Gly Ile Ile Ser
Leu Asn His Val Arg Gln Val Ile Gln His Asp Gly Arg Asn

Gln Glu Lys Leu Lys Lys Phe Met Ile Arg Ile Gly Val Phe Ser
Gly Leu Tyr Leu Val Pro Leu Val Thr Leu Leu Gly Cys Tyr
Val Tyr Glu Gln Val Asn Arg Ile Thr Trp Glu Ile Thr Trp Val
Ser Asp His Cys Arg Gln Tyr His Ile Pro Cys Pro Tyr Gln Ala
Lys Ala Lys Ala Arg Pro Glu Leu Ala Leu Phe Met Ile Lys Tyr
Leu Met Thr Leu Ile Val Gly Ile Ser Ala Val Phe Trp Val Gly
Ser Lys Lys Thr Cys Thr Glu Trp Ala Gly Phe Phe Lys Arg
Asn Arg Lys Arg Asp Pro Ile Ser Glu Ser Arg Arg Val Leu
Gln Glu Ser Cys Glu Phe Phe Leu Lys His Asn Ser Lys Val
Lys His Lys Lys Lys His Tyr Lys Pro Ser Ser His Lys Leu Lys
Val Ile Ser Lys Ser Met Gly Thr Ser Thr Gly Ala Thr Ala Asn
His Gly Thr Ser Ala Val Ala Ile Thr Ser His Asp Tyr Leu Gly
Gln Glu Thr Leu Thr Glu Ile Gln Thr Ser Pro Glu Thr Ser Met
Arg Glu Val Lys Ala Asp Gly Ala Ser Thr Pro Arg Leu Arg
Glu Gln Asp Cys Gly Glu Pro Ala Ser Pro Ala Ala Ser Ile Ser
Arg Leu Ser Gly Glu Gln Val Asp Gly Lys Gly Gln Ala Gly Ser
Val Ser Glu Ser Ala Arg Ser Glu Gly Arg Ile Ser Pro Lys Ser
Asp Ile Thr Asp Thr Gly Leu Ala Gln Ser Asn Asn Leu Gln
Val Pro Ser Ser Ser Glu Pro Ser Ser Leu Lys Gly Ser Thr Ser
Leu Leu Val His Pro Val Ser Gly Val Arg Lys Glu Gln Gly Gly
Gly Cys His Ser Asp Thr

[72] <210> 38 <211> 773 <212> DNA <213> Murinae gen.
sp.

73] ctgaggtgctagcaccagcctggttgtctctggcgggcctgaagcaagcatg-
gatcaagaggctgtgggcaacgttgtgctcctggcccttgtcaccct-
catcagcgtgggtccagaatgcgttctttgccacaaaggaggatgaaag-
caaggcgcataatgggagaagcttcagaggaccgggactcttgc-
ctttgagcgggtctacactgccaaccagaactgcgtagatgcgtaccc-
cactttccttgtgggtactctggactgcaggactactttgcagccaagtccct-
gcagccttcgccggactgatgtacctgtttgtgaggcaaaaatactttgtcggc-
tatctgggagagagaactcagagcaccctggctacatcttcggcaagcg-
gatcatcctgttcctgttcctcatgtccttcgccgggatactcaaccattacct-
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gatctccccgctgcttctcatcccctgattgctggagacagagaaggacgct-
caccagatcaatagagacgcatcataacgcaacgccgcgaaggcttctgctc-
ctcttcaagctgtagatgctgtcaatcttgctgccctcggggctctgtggcatc-
cgttaactttgcttttccgggaagaaaaatgtcttgctgaagctccaccctc-
gaatgcggcgggtgggccaggatttatgtctacatccagcctatacttctcctgg
2

274] <210> 39 <211> 852 <212> DNA <213> Murinae gen.
sp.

275] ggaaggctgaggtgctagcaccagcctggttgtctctggcgggcctgaag-
caagcatggatcaagaggctgtgggcaacgttgtgctcctggcccttgtcacc-
ctcatcagcgtgggtccagaatgtgtttttgccactatgtggagcatgaaag-
caatgcgcataatgggagaagcttcagaggaccgggactcttgc-
ctttgagcgggtctacactgccaaccagaactgcgtagatgcgtaccc-

cactttccttggtactctggactgcaggactactttgcagccaagtcctgc-
cgcttcgccggactgatgtacctgtttgtgaggcaaaaatactttgtcggc-
tatctgggagagagaactcagagcacccctggctacatcttcggcaagcg-
gatcatcctgttcctgttcctcatgtccttcgccgggataactcaaccattac-
catcttcttcttcggaagcgactttgagaactacatcagaacggtaagcacgac-
gatctccccgctgcttctcatcccctgattgctggagacagagaaggacgct-
caccagatcaatagagacgcatcataacgcaacgccgcgaaggcttctgctc-
ctcttcaagctgtagatgctgtcaatcttgctgccctcggggctctgtggcatc-
cgttaactttgcttttccgggaagaaaaatgtcttgtgctagctccaccctc-
gaatgcggcggtggcccaggatttattgtctacatccagcctatacttctcctg-
gcttatcctgctttctgaagatgtcttgtaatcagacacgtgttttcc-
taaaataaagggtatagacaaaattt

276] <210> 40 <211> 161 <212> PRT <213> Murinae gen.
sp.

277] Met Asp Gln Glu Ala Val Gly Asn Val Val Leu Leu Ala Leu
Val Thr Leu Ile Ser Val Val Gln Asn Val Phe Phe Ala His Tyr
Val Glu His Glu Ser Asn Ala His Asn Gly Arg Ser Phe Gln
Arg Thr Gly Thr Leu Ala Phe Glu Arg Val Tyr Thr Ala Asn
Gln Asn Cys Val Asp Ala Tyr Pro Thr Phe Leu Val Val Leu
Trp Thr Ala Gly Leu Leu Cys Ser Gln Val Pro Ala Ala Phe Ala
Gly Leu Met Tyr Leu Phe Val Arg Gln Lys Tyr Phe Val Gly
Tyr Leu Gly Glu Arg Thr Gln Ser Thr Pro Gly Tyr Ile Phe Gly
Lys Arg Ile Ile Leu Phe Leu Phe Leu Met Ser Phe Ala Gly Ile

Leu Asn His Tyr Leu Ile Phe Phe Phe Gly Ser Asp Phe Glu
Asn Tyr Ile Arg Thr Val Ser Thr Thr Ile Ser Pro Leu Leu Leu
Ile Pro

278] <210> 41 <211> 873 <212> DNA <213> Homo sapiens

279] acttccccttcctgtacagggcagggttggtgcagctggaggcagagcagtc-
ctctctgggggagcctgaagcaaactggatcaagaaactgtaggcaat-
gttgtcctgttggccatcgtcaccctcatcagcgtgggtccagaatg-
gattctttgcccataaagtggagcacgaaagcaggaccagaatgggag-
gagcttcagaggaccggaacacttgcctttgagcgggtctacactgc-
caaccagaactgtgtagatgcgtaccccactttcctcgtgtgctctgggtct-
gcggggctactttgcagccaagttcctgctgcgtttgctggactgatg-
tacttgtttgtagggcaaaagtactttgtcgggttacctaggagagagaacgca-
gagcaccctggctacatatattgggaaacgcatcatactcttcctgttcctcat-
gtccgttgctggcatattcaactattacctcatcttctttttcggaagt-
gactttgaaaactacataaagacgatctccaccaccatctcccctctacttct-
cattccctaactctctgctgaatatgggggttggtgttctcatctaatcaataccta-
caagtcataaattcagctcttgagagcattctgctcttcttttagatggctg-
taaattctattggccatctgggcttcacagcttgagttaaccttgcttttccgggaa-
caaatgatgtcatgtcagctccgccccttgaacatgaccgtggccc-
caaatttgctattcccatgcattttgtttgtttcttacttatcctgttctctgaagat-
gttttgtagaccagggtttgtgttttcttaaaataaaatgcagagacatgtttt

280] <210> 42 <211> 161 <212> PRT <213> Homo sapiens

81] Met Asp Gln Glu Thr Val Gly Asn Val Val Leu Leu Ala Ile Val
Thr Leu Ile Ser Val Val Gln Asn Gly Phe Phe Ala His Lys Val
Glu His Glu Ser Arg Thr Gln Asn Gly Arg Ser Phe Gln Arg
Thr Gly Thr Leu Ala Phe Glu Arg Val Tyr Thr Ala Asn Gln
Asn Cys Val Asp Ala Tyr Pro Thr Phe Leu Ala Val Leu Trp
Ser Ala Gly Leu Leu Cys Ser Gln Val Pro Ala Ala Phe Ala Gly
Leu Met Tyr Leu Phe Val Arg Gln Lys Tyr Phe Val Gly Tyr
Leu Gly Glu Arg Thr Gln Ser Thr Pro Gly Tyr Ile Phe Gly Lys
Arg Ile Ile Leu Phe Leu Phe Leu Met Ser Val Ala Gly Ile Phe
Asn Tyr Tyr Leu Ile Phe Phe Phe Gly Ser Asp Phe Glu Asn
Tyr Ile Lys Thr Ile Ser Thr Thr Ile Ser Pro Leu Leu Leu Ile
Pro

282] <210> 43 <211> 803 <212> DNA <213> Murinae gen.
sp.

283] ttcagctttatgggttggttccttgactgcattttctgtcagttaactaaactcca-
gactcatggattttctcgaccagaaaatcagactattttcctgaataatctacta-
gaaacttttacggaacacatttcatgtttcctttgaagagttaagagaagaaag-
tatttgtaagaacaggaaaagaaacaaataactttgcaaataaactggctgct-
gctgtgaccacatctgaatagcaaaggcgatcgatcaagcgctgcgga-
caaaaggcctcctgtaagctgcactgcctgacaatggtaagctccaatggctc-
ccagtgcccttatgacgactcctttaagtacactctgtacgggtgcat-
gttcagcatgggtcttcgtgcttgggctgatatccaactgtgttgcgatata-
cattttcatctgtgccctcaaagtgagaaatgaaactacaacgtacatgattaac-

ctggcaatgtcagatttacttttcgtctttactttgccatttcggattttttactttg-
caacacggaattggccatttggagatctactctgtaagatttcagtaatgct-
gttttacaccaatatgtatgggaagcattctgttcttaacctgtatcagtgt-
gatcgatttctggcaattgtctacccatttaagtcaaagactttaagaaac-
gaaacgaaaatgcaaagaatcgtttgcattgcctgtgtggttcacagt-
gatgggaggaagtgcgctgcagttttcttcagtcgacccactctcaggggaa-
caatactcagaagct

284] <210> 44 <211> 1849 <212> DNA <213> Murinae gen.
sp.

285] agagacagcccatctcacaatacagctggcaacctccgaaaggcctctc-
cattcagcaagcgcgacaatgcttaggaatttatctgggatcccttaaacgact-
gcctatcgccgtccggaatcaatgtagaaatacaaagtttgagaataaaaa-
gaaggaagaagtacccgaggacgacggggcggacggacgcacggcgagt-
gtttgtgactgaagtaaagctggtttggaccctggcggctgaagcacaagtttc-
cacgcggactgggtctgggtccgacttggaacagtttttccttacactttcagctt-
tatggggttggttccttgactgcattttctgtcagttaactaaactccagact-
catggattttctcgaccagaaaatcagactattttcctgaataatctacta-
gaaacttttacggaacacatttcattgtttccttgaagagttaagagaagaag-
tatttgtaagaacaggaaaagaaacaaataactttgcaaataaactggctgct-
gctgtgaccacatctgaatagcaaaggcgatcgatcaagcgctgcgga-
caaaggcctcctgtaagctgcactgcctgacaatggtaagctccaatggctc-
ccagtgcccttatgacgactcctttaagtacactctgtacgggtgcat-
gttcagcatgggtcttcgtgcttgggctgatatccaactgtgttgcgatata-

cattttcatctgtgccctcaaagtgagaaatgaaactacaacgtacatgattaac-
ctggcaatgtcagatttacttttcgtctttactttgccatttcggattttttactttg-
caacacggaattggccatttggagatctactctgtaagatttcagtaatgct-
gttttacaccaatatgtatggaagcattctgttcttaacctgtatcagtgtagatc-
gatttctggcaattgtctacccatttaagtcaaagactttaagaacgaaac-
gaaatgcaaagatcgtttgcattgctgtgtgggtcacagtgatgggaggaagt-
gcgcctgcagttttctttcagtcgaccactctcaggggaacaataacctca-
gaagcctgctttgagaactttccagcggccacatggaaaact-
tatctctccaggattgtgattttcattgaaatagtgggcttttttatccctct-
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cattaagtagaagcaaaatgaacaaaactaagggttttaaaaatgatttttgtc-
cacttggtcatcttctgttttctgttttgtgccctacaacatcaacctcattttg-
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taacgtgttttttcctcattaaaaaaaaaaaaaactcc

86] <210> 45 <211> 316 <212> PRT <213> Murinae gen.

sp.

87] Asp Asp Ser Phe Lys Tyr Thr Leu Tyr Gly Cys Met Phe Ser
Met Val Phe Val Leu Gly Leu Ile Ser Asn Cys Val Ala Ile Tyr
Ile Phe Ile Cys Ala Leu Lys Val Arg Asn Glu Thr Thr Thr Tyr
Met Ile Asn Leu Ala Met Ser Asp Leu Leu Phe Val Phe Thr
Leu Pro Phe Arg Ile Phe Tyr Phe Ala Thr Arg Asn Trp Pro
Phe Gly Asp Leu Leu Cys Lys Ile Ser Val Met Leu Phe Tyr
Thr Asn Met Tyr Gly Ser Ile Leu Phe Leu Thr Cys Ile Ser Val
Asp Arg Phe Leu Ala Ile Val Tyr Pro Phe Lys Ser Lys Thr Leu
Arg Thr Lys Arg Asn Ala Lys Ile Val Cys Ile Ala Val Trp Phe
Thr Val Met Gly Gly Ser Ala Pro Ala Val Phe Phe Gln Ser Thr
His Ser Gln Gly Asn Asn Thr Ser Glu Ala Cys Phe Glu Asn
Phe Pro Ala Ala Thr Trp Lys Thr Tyr Leu Ser Arg Ile Val Ile
Phe Ile Glu Ile Val Gly Phe Phe Ile Pro Leu Ile Leu Asn Val
Thr Cys Ser Ser Met Val Leu Arg Thr Leu Asn Lys Pro Val
Thr Leu Ser Arg Ser Lys Met Asn Lys Thr Lys Val Leu Lys
Met Ile Phe Val His Leu Val Ile Phe Cys Phe Cys Phe Val Pro
Tyr Asn Ile Asn Leu Ile Leu Tyr Ser Leu Met Arg Thr Gln
Thr Phe Val Asn Cys Ser Val Val Ala Ala Val Arg Thr Met
Tyr Pro Ile Thr Leu Cys Ile Ala Val Ser Asn Cys Cys Phe Asp
Pro Ile Val Tyr Tyr Phe Thr Ser Asp Thr Ile Gln Asn Ser Ile
Lys Met Lys Asn Trp Ser Val Arg Arg Ser Asp Ser Arg Phe
Ser Glu Val Gln Gly Thr Glu Asn Phe Ile Gln

288]

289] <210> 46 <211> 1035 <212> DNA <213> Homo sapi-
ens

290] atggtaagcgttaacagctcccactgcttctataatgactcctttaagta-
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caacttacatgattaacttggcaatgtcagacttgctttttgtttttactttacc-
cttcaggattttttacttcacaacacggaattggccatttggagatttactttgtaa-
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caatgcctcagaagcctgctttgaaaattttccagaagccacatggaaaa-
cataatctctcaaggattgtaattttcatcgaaatagtgggattttttattcctc-
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catttgatcatattctgtttctgttttgttccttacaatatcaatcttattt-
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taaaaagtaagatatttgacaatgaatctgctgcctga

291] <210> 47 <211> 344 <212> PRT <213> Homo sapiens

292] Met Val Ser Val Asn Ser Ser His Cys Phe Tyr Asn Asp Ser
Phe Lys Tyr Thr Leu Tyr Gly Cys Met Phe Ser Met Val Phe
Val Leu Gly Leu Ile Ser Asn Cys Val Ala Ile Tyr Ile Phe Ile
Cys Val Leu Lys Val Arg Asn Glu Thr Thr Thr Tyr Met Ile
Asn Leu Ala Met Ser Asp Leu Leu Phe Val Phe Thr Leu Pro
Phe Arg Ile Phe Tyr Phe Thr Thr Arg Asn Trp Pro Phe Gly
Asp Leu Leu Cys Lys Ile Ser Val Met Leu Phe Tyr Thr Asn
Met Tyr Gly Ser Ile Leu Phe Leu Thr Cys Ile Ser Val Asp Arg
Phe Leu Ala Ile Val Tyr Pro Phe Lys Ser Lys Thr Leu Arg Thr
Lys Arg Asn Ala Lys Ile Val Cys Thr Gly Val Trp Leu Thr Val
Ile Gly Gly Ser Ala Pro Ala Val Phe Val Gln Ser Thr His Ser
Gln Gly Asn Asn Ala Ser Glu Ala Cys Phe Glu Asn Phe Pro
Glu Ala Thr Trp Lys Thr Tyr Leu Ser Arg Ile Val Ile Phe Ile
Glu Ile Val Gly Phe Phe Ile Pro Leu Ile Leu Asn Val Thr Cys
Ser Ser Met Val Leu Lys Thr Leu Thr Lys Pro Val Thr Leu
Ser Arg Ser Lys Ile Asn Lys Thr Lys Val Leu Lys Met Ile Phe
Val His Leu Ile Ile Phe Cys Phe Cys Phe Val Pro Tyr Asn Ile
Asn Leu Ile Leu Tyr Ser Leu Val Arg Thr Gln Thr Phe Val
Asn Cys Ser Val Val Ala Ala Val Arg Thr Met Tyr Pro Ile Thr
Leu Cys Ile Ala Val Ser Asn Cys Cys Phe Asp Pro Ile Val Tyr
Tyr Phe Thr Ser Asp Thr Ile Gln Asn Ser Ile Lys Met Lys Asn
Trp Ser Val Arg Arg Ser Asp Phe Arg Phe Ser Glu Val His

Gly Ala Glu Asn Phe Ile Gln His Asn Leu Gln Thr Leu Lys
Ser Lys Ile Phe Asp Asn Glu Ser Ala Ala

293] <210> 48 <211> 814 <212> DNA <213> Murinae gen.
sp.

294] gagcgcgcgtaagatggcactaccattttctgtcaaccttcgggggtgcgtaatg-
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cttcagggagctcgatccccaacagccagtcaccacctctgtcccctcttcact-
gttggtcgtcagactgcctgagtggaacagcaggctggtcgcgttg-
tattttcacttccttcctctgactggcttgctcttgtctctcagtcctttcatc-
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gactcttgtggacacaggccgtgggtggcttgtcagaccttaagggtccaggc-
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gctgagtaatgagcagcttattacacacaatgggaagagggggcaga-
gagggtgtgtcgggttgagtcctcggctgggactgaagtttgccataagtagtg-
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295] <210> 49 <211> 1164 <212> DNA <213> Murinae gen.
sp.

296] ggtcgcctatttcttgggtgcgtgacatcaccgagaagatggacatactgggcac-

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gaaactccagacggacggactcaaggagtgcattatcttctgcgtgcgggag-
gagcctgtgggtgttcttgcgcgctgaggaggactttgtgtcttacacacctcga-
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gctgagaatctggagctggccatccagaaagagatccatgactttgcc-
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gataccaccgcctccccttgccagagcaaggggccccctggaagc-
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gccaaaccttgcccatggagcagtttcaggtgatccagggcttcatctg-
taaggtgccacaggggaagaaaatggtggaggaggtggatcgagc-
gatcagtgctgtgcagagttgcatgacctgaaggaggaggtcc-
taaaaaaccagaggaggctggaaagcttcaggccagagagc-
cggggacaggaatgtggtagtcagcaagctgtccagcagagggcgctgtg-
gagcctggagctgtacttctatctgctcctatttaactactatctgcat-
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297] <210> 50 <211> 388 <212> PRT <213> Murinae gen.
sp.

298] Gly Arg Tyr Phe Leu Val Arg Asp Ile Thr Glu Lys Met Asp Ile
Leu Gly Thr Leu Lys Ser Cys Gly Ala Pro Asn Phe Arg Gln
Val Arg Gly Gly Leu Pro Val Phe Gly Met Gly Gln Pro Ser Leu
Leu Gly Phe Arg Arg Val Leu Gln Lys Leu Gln Thr Asp Gly
Leu Lys Glu Cys Ile Ile Phe Cys Val Arg Glu Glu Pro Val Val
Phe Leu Arg Ala Glu Glu Asp Phe Val Ser Tyr Thr Pro Arg
Asp Lys Glu Ser Leu His Glu Asn Leu Arg Asp Pro Ser Pro
Gly Val Lys Ala Glu Asn Leu Glu Leu Ala Ile Gln Lys Glu Ile
His Asp Phe Ala Gln Leu Arg Asp Asn Val Tyr His Val Tyr
His Asn Thr Glu Asp Leu Arg Gly Glu Pro His Thr Val Ala Ile
Arg Gly Glu Asp Gly Val Cys Val Thr Glu Glu Val Phe Lys
Arg Pro Leu Phe Leu Gln Pro Thr Tyr Arg Tyr His Arg Leu
Pro Leu Pro Glu Gln Gly Ala Pro Leu Glu Ala Gln Phe Asp
Ala Phe Val Ser Val Leu Arg Glu Thr Pro Ser Leu Leu Pro
Leu Arg Asp Asn His Gly Pro Leu Pro Ala Leu Leu Phe Ser
Cys Gln Ser Gly Val Gly Arg Thr Asn Leu Gly Met Val Leu
Gly Thr Leu Val Met Phe His His Ser Arg Thr Thr Ser Gln
Leu Glu Ala Ala Ser Pro Leu Ala Lys Pro Leu Pro Met Glu
Gln Phe Gln Val Ile Gln Gly Phe Ile Cys Lys Val Pro Gln Gly
Lys Lys Met Val Glu Glu Val Asp Arg Ala Ile Ser Ala Cys Ala
Glu Leu His Asp Leu Lys Glu Glu Val Leu Lys Asn Gln Arg

Arg Leu Glu Ser Phe Arg Pro Glu Ser Arg Gly Gln Glu Cys
Gly Ser Gln Gln Ala Val Gln Gln Arg Ala Leu Trp Ser Leu Glu
Leu Tyr Phe Tyr Leu Leu Leu Phe Asn Tyr Tyr Leu His Glu
Gln Tyr Pro Leu Ala Phe Ala Leu Ser Phe Ser Arg Trp Leu
Cys Thr His Pro Glu Leu Tyr Arg Leu Leu Val Glu Leu Asn
Ser Val Gly Pro Leu Val Pro Gly Asp Leu Ile Ala Lys Gly Ser

299] <210> 51 <211> 4303 <212> DNA <213> Homo sapi-
ens

300] ggctgctggcagactatgggtacaacggccagcacagcccagcagacg-
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cacgtacaactgcaaggaggaggtccagatccatgatgagctgctcaaggct-
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taaaatgggagaataataacttgcctacctacctcacaggggtgttgag-
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taaattgtga

301] <210> 52 <211> 861 <212> PRT <213> Homo sapiens

302] Gly Cys Trp Gln Thr Met Gly Thr Thr Ala Ser Thr Ala Gln
Gln Thr Val Ser Ala Gly Thr Pro Phe Glu Gly Leu Gln Gly Ser
Gly Thr Met Asp Ser Arg His Ser Val Ser Ile His Ser Phe Gln
Ser Thr Ser Leu His Asn Ser Lys Ala Lys Ser Ile Ile Pro Asn
Lys Val Ala Pro Val Val Ile Thr Tyr Asn Cys Lys Glu Glu Phe
Gln Ile His Asp Glu Leu Leu Lys Ala His Tyr Thr Leu Gly Arg
Leu Ser Asp Asn Thr Pro Glu His Tyr Leu Val Gln Gly Arg
Tyr Phe Leu Val Arg Asp Val Thr Glu Lys Met Asp Val Leu
Gly Thr Val Gly Ser Cys Gly Ala Pro Asn Phe Arg Gln Val
Gln Gly Gly Leu Thr Val Phe Gly Met Gly Gln Pro Ser Leu Ser
Gly Phe Arg Arg Val Leu Gln Lys Leu Gln Lys Asp Gly His
Arg Glu Cys Val Ile Phe Cys Val Arg Glu Glu Pro Val Leu
Phe Leu Arg Ala Asp Glu Asp Phe Val Ser Tyr Thr Pro Arg
Asp Lys Gln Asn Leu His Glu Asn Leu Gln Gly Leu Gly Pro
Gly Val Arg Val Glu Ser Leu Glu Leu Ala Ile Arg Lys Glu Ile
His Asp Phe Ala Gln Leu Ser Glu Asn Thr Tyr His Val Tyr
His Asn Thr Glu Asp Leu Trp Gly Glu Pro His Ala Val Ala Ile
His Gly Glu Asp Asp Leu His Val Thr Glu Glu Val Tyr Lys
Arg Pro Leu Phe Leu Gln Pro Thr Tyr Arg Tyr His Arg Leu

Pro Leu Pro Glu Gln Gly Ser Pro Leu Glu Ala Gln Leu Asp
Ala Phe Val Ser Val Leu Arg Glu Thr Pro Ser Leu Leu Gln
Leu Arg Asp Ala His Gly Pro Pro Pro Ala Leu Val Phe Ser
Cys Gln Met Gly Val Gly Arg Thr Asn Leu Gly Met Val Leu
Gly Thr Leu Ile Leu Leu His Arg Ser Gly Thr Thr Ser Gln Pro
Glu Ala Ala Pro Thr Gln Ala Lys Pro Leu Pro Met Glu Gln
Phe Gln Val Ile Gln Ser Phe Leu Arg Met Val Pro Gln Gly Arg
Arg Met Val Glu Glu Val Asp Arg Ala Ile Thr Ala Cys Ala Glu
Leu His Asp Leu Lys Glu Val Val Leu Glu Asn Gln Lys Lys
Leu Glu Gly Ile Arg Pro Glu Ser Pro Ala Gln Gly Ser Gly Ser
Arg His Ser Val Trp Gln Arg Ala Leu Trp Ser Leu Glu Arg
Tyr Phe Tyr Leu Ile Leu Phe Asn Tyr Tyr Leu His Glu Gln
Tyr Pro Leu Ala Phe Ala Leu Ser Phe Ser Arg Trp Leu Cys
Ala His Pro Glu Leu Tyr Arg Leu Pro Val Thr Leu Ser Ser Ala
Gly Pro Val Ala Pro Arg Asp Leu Ile Ala Arg Gly Ser Leu Arg
Glu Asp Asp Leu Val Ser Pro Asp Ala Leu Ser Thr Val Arg
Glu Met Asp Val Ala Asn Phe Arg Arg Val Pro Arg Met Pro
Ile Tyr Gly Thr Ala Gln Pro Ser Ala Lys Ala Leu Gly Ser Ile
Leu Ala Tyr Leu Thr Asp Ala Lys Arg Arg Leu Arg Lys Val
Val Trp Val Ser Leu Arg Glu Glu Ala Val Leu Glu Cys Asp
Gly His Thr Tyr Ser Leu Arg Trp Pro Gly Pro Pro Val Ala Pro
Asp Gln Leu Glu Thr Leu Glu Ala Gln Leu Lys Ala His Leu
Ser Glu Pro Pro Pro Gly Lys Glu Gly Pro Leu Thr Tyr Arg Phe

Gln Thr Cys Leu Thr Met Gln Glu Val Phe Ser Gln His Arg
Arg Ala Cys Pro Gly Leu Thr Tyr His Arg Ile Pro Met Pro
Asp Phe Cys Ala Pro Arg Glu Glu Asp Phe Asp Gln Leu Leu
Glu Ala Leu Arg Ala Ala Leu Ser Lys Asp Pro Gly Thr Gly
Phe Val Phe Ser Cys Leu Ser Gly Gln Gly Arg Thr Thr Thr
Ala Met Val Val Ala Val Leu Ala Phe Trp His Ile Gln Gly Phe
Pro Glu Val Gly Glu Glu Glu Leu Val Ser Val Pro Asp Ala Lys
Phe Thr Lys Gly Glu Phe Gln Val Val Met Lys Val Val Gln
Leu Leu Pro Asp Gly His Arg Val Lys Lys Glu Val Asp Ala
Ala Leu Asp Thr Val Ser Glu Thr Met Thr Pro Met His Tyr
His Leu Arg Glu Ile Ile Ile Cys Thr Tyr Arg Gln Ala Lys Ala
Ala Lys Glu Ala Gln Glu Met Arg Arg Leu Gln Leu Arg Ser
Leu Gln Tyr Leu Glu Arg Tyr Val Cys Leu Ile Leu Phe Asn
Ala Tyr Leu His Leu Glu Lys Ala Asp Ser Trp Gln Arg Pro
Phe Ser Thr Trp Met Gln Glu Val Ala Ser Lys Ala Gly Ile Tyr
Glu Ile Leu Asn Glu Leu Gly Phe Pro Glu Leu Glu Ser Gly
Glu Asp Gln Pro Phe Ser Arg Leu Arg Tyr Arg Trp Gln Glu
Gln Ser Cys Ser Leu Glu Pro Ser Ala Pro Glu Asp Leu Leu

03] <210> 53 <211> 736 <212> DNA <213> Murinae gen.
sp.

04] gtgatccaggatccgaagaggcccggagcaggagcatg-
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gttggcgagtgcggcacgggccagactctacttccgctcgggccagacttgc-

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ctcggccgcatgagtacctgtccccagcggatctccccaagaattgggactg-
gagaaatgtgaacggtgtcaactatgccagcgtcaccaggaaccagcacatc-
ccacagtactgtggttcctgctgggcccacggcagcaccagtgccatggca-
gaccgaatcaacatcaagaggaaagggtgcatggccctccatcctgctgtccg-
tacagaatgtcattgactgtggcaatgctggctcttgtgaagggggcaatgac-
cttcgggtgtgggagtatgccacaagcatggcatccccgatgagacctgcaa-
caactaccaggcaaggaccaagactgtgacaagtttaaccagtgtgggacct-
gcactgaattcaaagagtgtcacaccatccagaattacaccctctgga-
gagtgggtgattacgggtccctgtccggggagggagaagatgatggcgagatc-
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taactacactggggggcatctatgctga

305] <210> 54 <211> 1404 <212> DNA <213> Murinae gen.
sp.

306] aaaggaccgggcgggcggtcccgagcgcgtgggcctgcgggtcgggtcaa-
gaggtcgaagggtgctgcgcgtgatccaggatccgaattggcccg-
gagcaggagcatggcgtcgtcgggggtcgggtgcagcagctgcccctggtgct-
gctgatgttgctgttggcgagtgcggcacggggccagactctacttc-
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Asn Leu Ala Ile Glu Glu His Cys Thr Phe Gly Asp Pro Ile Val

Claims

- 1] 1. An isolated nucleic acid molecule according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 or a fragment or analogue thereof which has the ability to stimulate or inhibit at least one biological activity selected from the group consisting of vasculogenesis, angiogenesis, vascular permeability, endothelial cell proliferation, endothelial cell differentiation, endothelial cell migration, and endothelial cell survival, or an isolated nucleic acid molecule which hybridizes to one of the foregoing sequences under stringent conditions.
- 2] 2. An isolated nucleic acid molecule which hybridizes to the compliment of a nucleic acid molecule according to Claim 1 under stringent conditions.
- 3] 3. An isolated siRNA molecule targeted to an isolated nucleic acid molecule according to Claims 1 or 2, wherein the isolated siRNA molecule is at least 19 base pairs long.
- 4] 4. An expression vector comprising the nucleic acid according to Claims 1 or 2.

- 5] 5. An expression vector according to Claim 4, wherein the nucleic acid is operatively associated with a regulatory nucleic acid controlling the expression of the polypeptide encoded by said nucleic acid.
- 6] 6. A host cell genetically engineered to contain a nucleic acid according to Claims 1 or 2.
- 7] 7. A host cell transfected with an expression vector according to Claims 4 or 5.
- 8] 8. A method of treating an angiogenesis-related condition in a cell, group of cells, or organism, comprising the step of administering an expression vector according to Claims 4 or 5 to the cell, group of cells, or organism.
- 9] 9. An antibody with specific reactivity to a nucleic acid according to Claims 1 or 2.
- 0] 10. An antibody according to Claim 9, wherein said antibody is a polyclonal antibody.
- 1] 11. An antibody according to Claim 9, wherein said antibody is a monoclonal antibody.
- 2] 12. An antibody according to any one of Claims 9-11, further comprising a detectable label.
- 3] 13. An antibody according to Claim 12, wherein the de-

tectable label is fluorescent.

- 4] 14.A transgenic, non-human animal which has been genetically engineered to contain a transgene comprising a nucleic acid according to Claims 1 or 2.
- 5] 15.A transgenic, non-human animal according to Claim 14, wherein the transgene is expressed.
- 6] 16.A pharmaceutical composition comprising a nucleic acid sequence according to Claims 1 or 2.
- 7] 17.A method of affecting vasculogenesis or angiogenesis in a cell, group of cells, or organism, comprising the step of administering a pharmaceutical composition according to Claim 16 to the cell, group of cells, or organism.
- 18] 18.A method according to Claim 17, wherein vasculogenesis or angiogenesis are increased.
- 19] 19.A method according to Claim 17, wherein vasculogenesis or angiogenesis are decreased.
- 20] 20.A method according to any one of Claims 17-19, wherein the cell, group of cells, or organism has an angiogenesis-related disorder.
- 21] 21.A method according to Claim 20, wherein the angiogenesis-related disorder is selected from the group con-

sisting of: cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

- 22] 22. An isolated polypeptide comprising a sequence of amino acids substantially corresponding to the amino acid sequence in any one of SEQ ID NO:s 3, 5, 8, 10, 13, 15, 18, 20, 22, 25, 27, 30, 32, 35, 37, 40, 42, 45, 47, 50, 52, 55, and 57 or a fragment or analogue thereof, said polypeptide having the ability to affect angiogenesis in a cell, a group of cells, or an organism.
- 23] 23. A host cell genetically engineered to express a polypeptide according to Claim 22.
- 24] 24. An antibody specifically reactive with a polypeptide according to Claim 22.
- 25] 25. An antibody according to Claim 24, wherein said an-

antibody is a polyclonal antibody.

- 26] 26. An antibody according to Claim 24, wherein said antibody is a monoclonal antibody.
- 27] 27. An antibody according to any one of Claims 24-26, further comprising a detectable label.
- 28] 28. An antibody according to Claim 27, wherein the detectable label is fluorescent.
- 29] 29. A transgenic, non-human animal which has been genetically engineered to contain a transgene comprising a nucleic acid which encodes a polypeptide according to Claim 22.
- 30] 30. The transgenic, non-human animal of Claim 29, wherein the transgene is expressed.
- 31] 31. A pharmaceutical composition comprising an isolated polypeptide according to Claim 22.
- 32] 32. A method of affecting vasculogenesis or angiogenesis in a cell, group of cells, or organism, comprising the step of administering a pharmaceutical composition according to Claim 31 to the cell, group of cells, or organism.
- 33] 33. A method according to Claim 32, wherein vasculogenesis or angiogenesis are increased.

- 34] 34.A method according to Claim 32, wherein vasculogenesis or angiogenesis are decreased.
- 35] 35.A method according to any one of Claims 32-34, wherein the cell, group of cells, or organism has an angiogenesis-related disorder.
- 36] 36.A method according to Claim 35, wherein the angiogenesis-related disorder is selected from the group consisting of: cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.
- 37] 37.A method of detecting an angiogenesis-related transcript in a cell in a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence according to any one

of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56, wherein an angiogenesis-related transcript is detected where hybridization is detected.

38] 38.A method according to Claim 37, wherein the polynucleotide comprises a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56.

39] 39.A method according to Claims 37 or 38, wherein the biological sample is a tissue sample.

40] 40.A method according to Claims 37 or 38, wherein the biological sample comprises isolated nucleic acids.

41] 41.A method according to Claim 40, wherein the nucleic acids are mRNA.

42] 42.A method according to Claims 37 or 38, further comprising the step of amplifying nucleic acids before the step of contacting the biological sample with the polynucleotide.

43] 43.A method according to Claims 37 or 38, wherein the polynucleotide is immobilized on a solid surface.

44] 44.A method of affecting at least one bioactivity selected from angiogenesis and vasculogenesis in a vertebrate

organism, said method comprising the step of administering to said organism an effective angiogenesis or vasculogenesis affecting amount of a nucleotide or polypeptide according to Claims 1 or 22.

45] 45.A method according to Claim 44, wherein said organism is a mammal.

46] 46.A method according to Claim 45, wherein said mammal is selected from the group consisting of mice, rats, rabbits, guinea pigs, cats, dogs, pigs, cows, monkeys, and humans.

47] 47.A method according to Claim 44, wherein vasculogenesis or angiogenesis is enhanced or increased.

48] 48.A method according to Claim 44, wherein vasculogenesis or angiogenesis is inhibited or decreased.

49] 49.A method according to one of Claims 44-48, wherein the organism has an angiogenesis-related disorder.

50] 50.A method according to Claim 49, wherein the angiogenesis-related disorder is selected from the group consisting of: cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardo-

sis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

- 51] 51.A transgenic increased angiogenesis laboratory animal comprising one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is upregulated.
- 52] 52.A transgenic decreased angiogenesis laboratory animal comprising one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is down regulated or absent.

Angiogenesis affecting polypeptides, proteins, and compositions, and methods of use thereof

Abstract

The present invention relates to polynucleotides and proteins associated with vasculogenesis- and angiogenesis-related disorders. The invention further relates to methods for the identification of compounds that modulate the expression of angiogenesis-related genes and gene products and to using such compounds as therapeutic agents in the treatment of angiogenesis-related disorders. The invention also relates to methods for the diagnostic evaluation, genetic testing and prognosis of angiogenesis-related disorders, and to methods and compositions for the treatment these disorders.

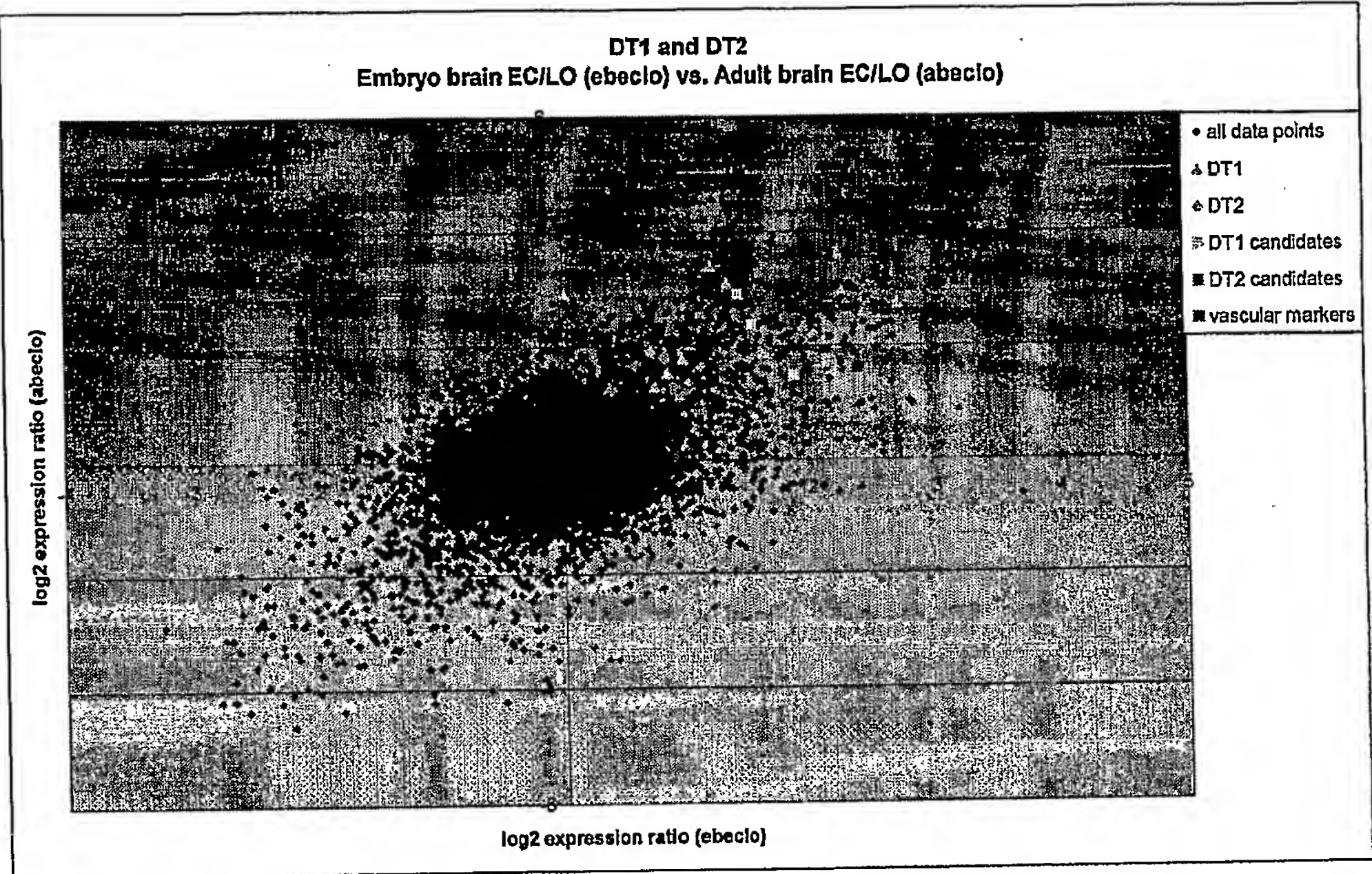


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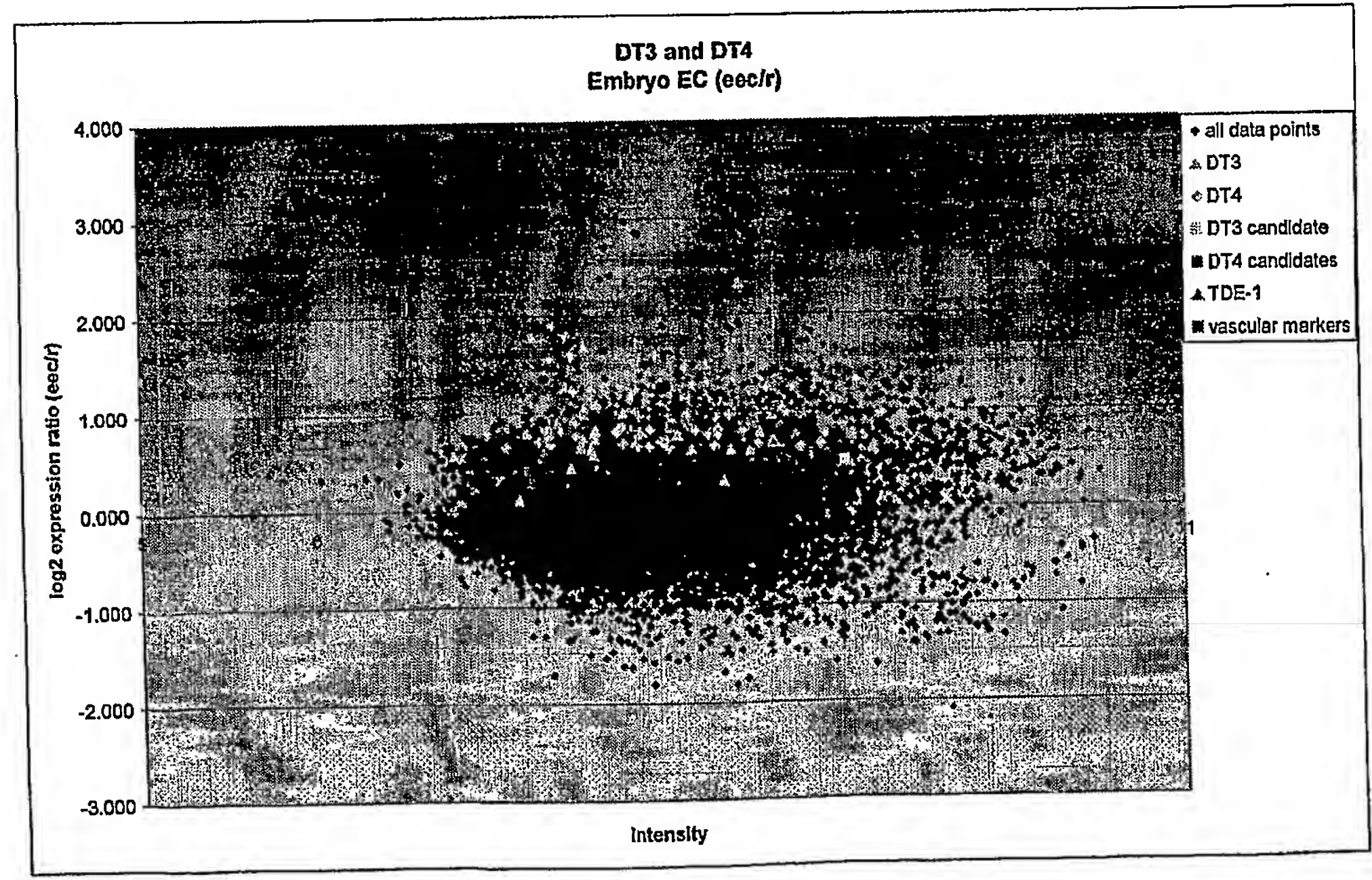


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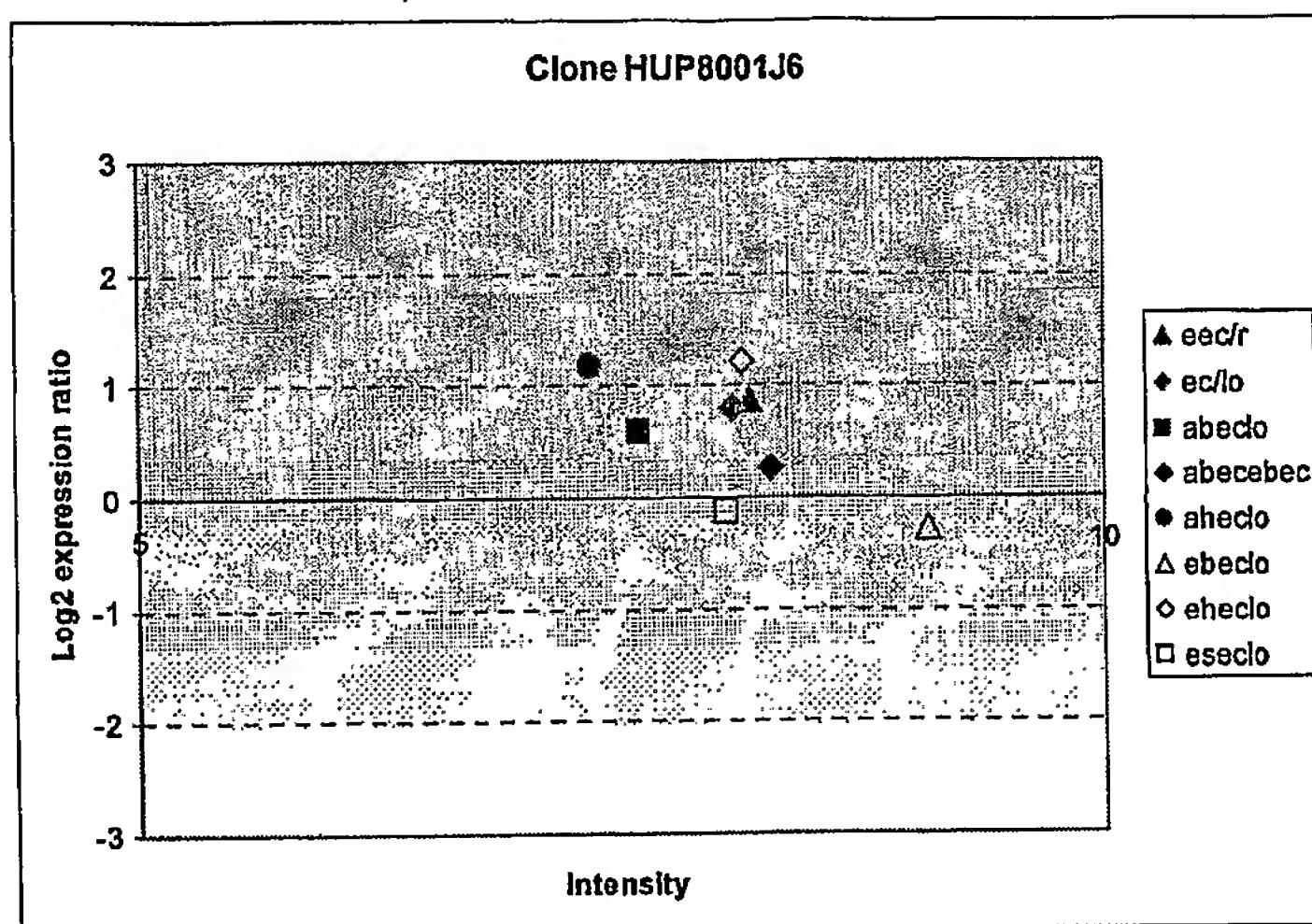


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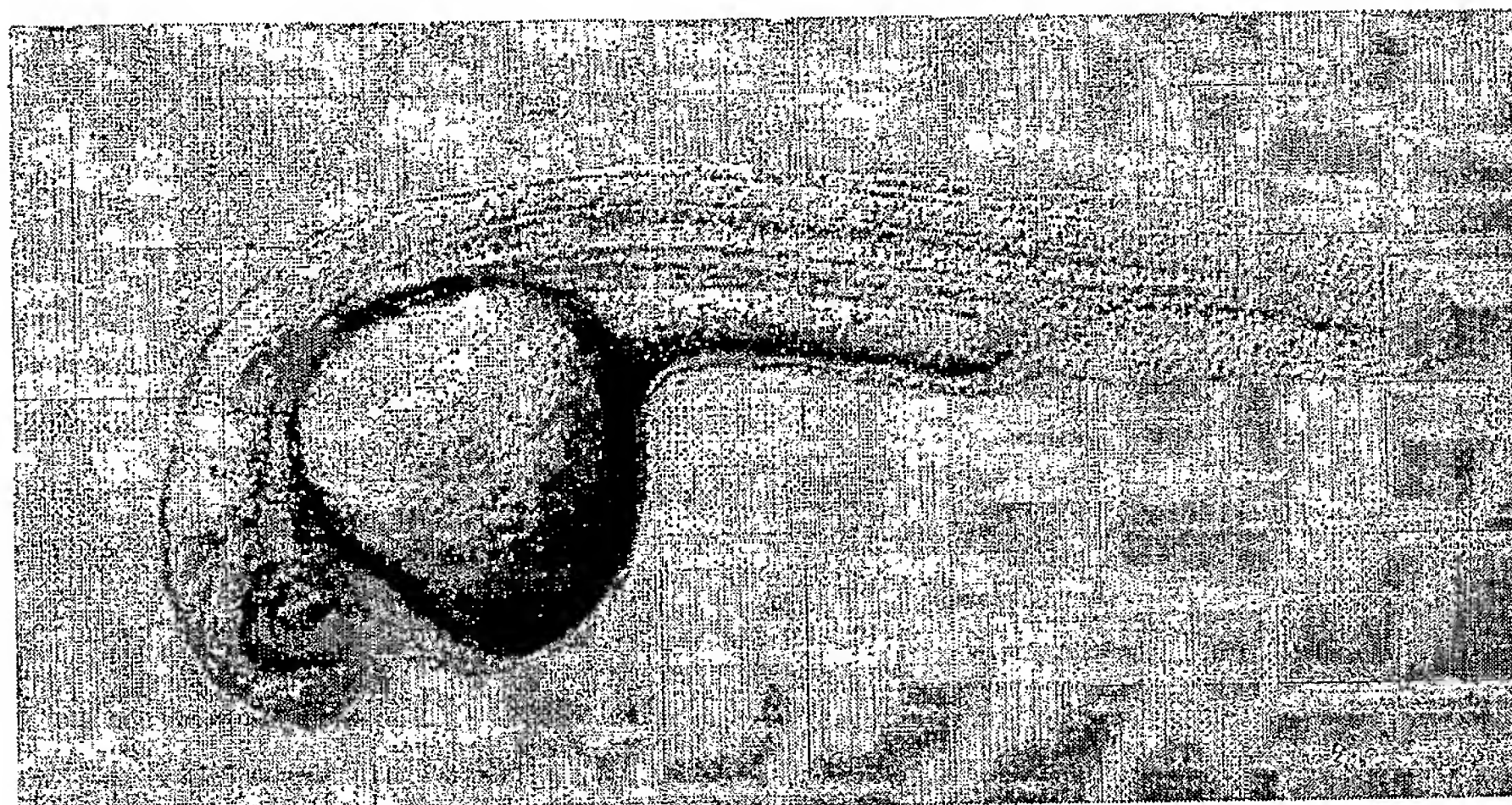


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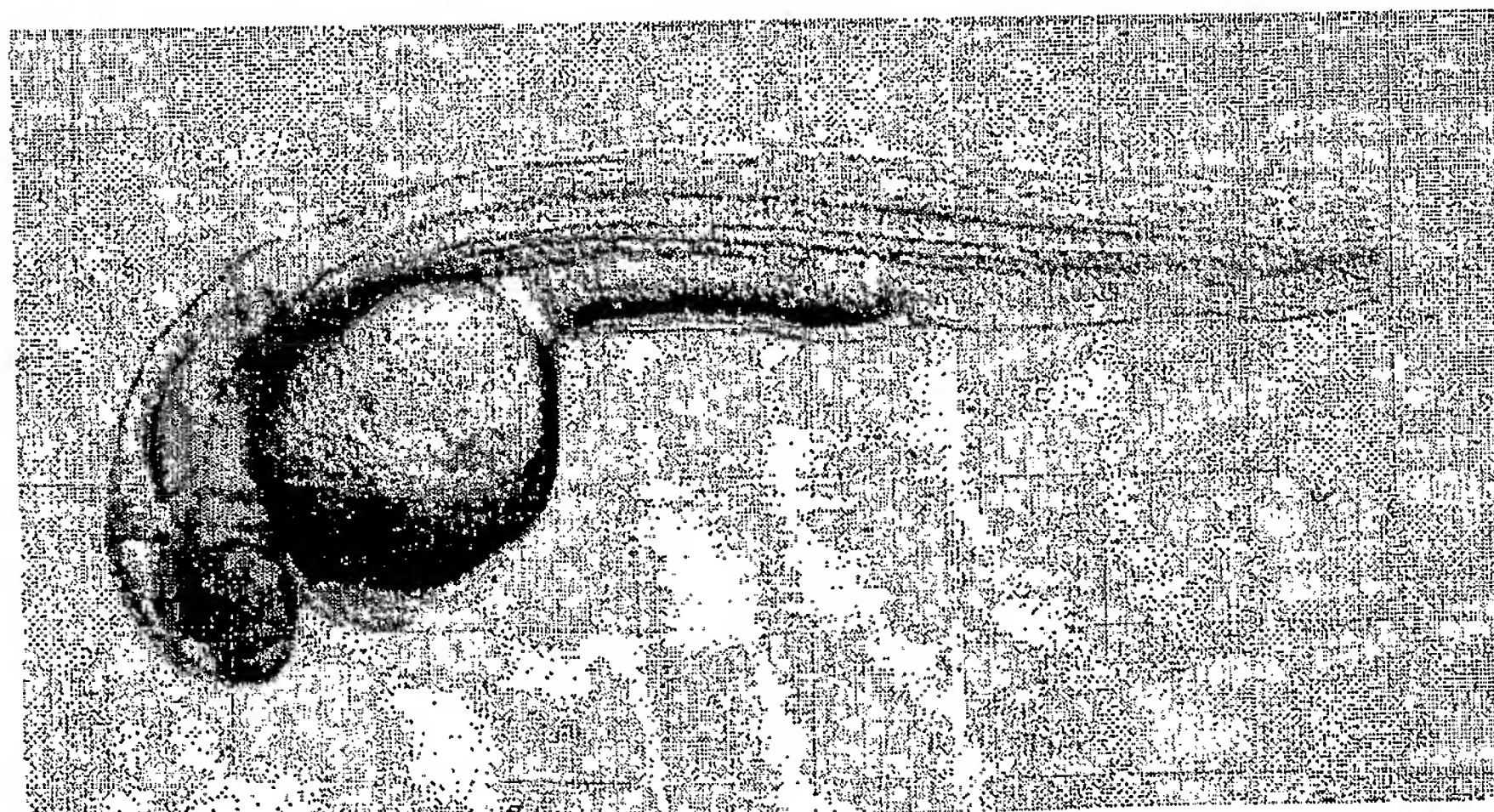


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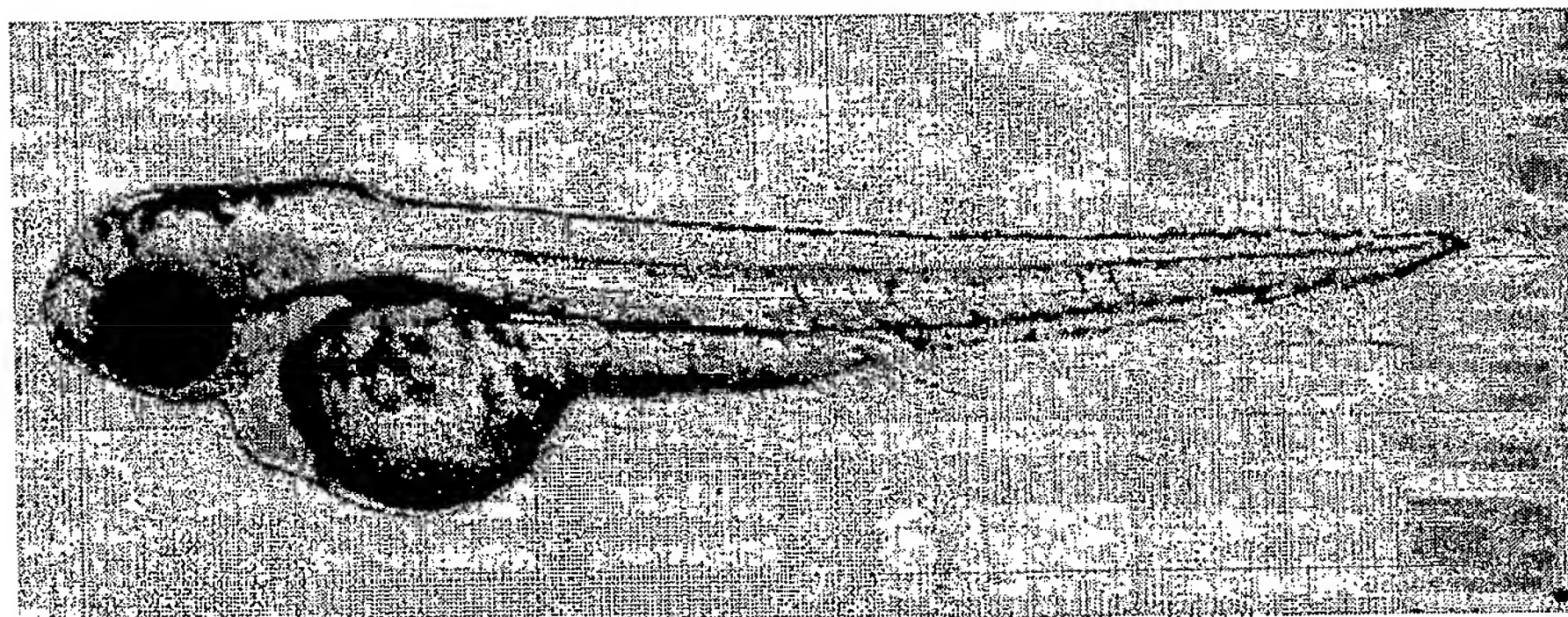


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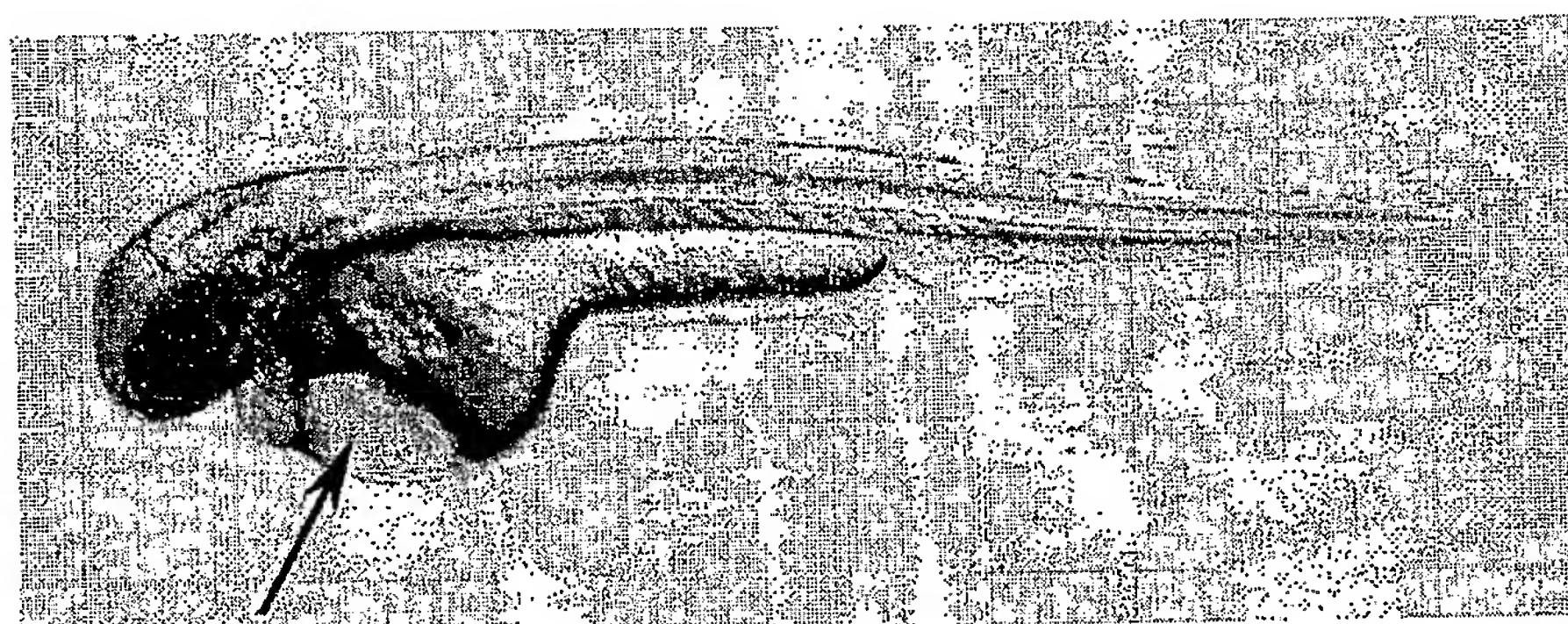


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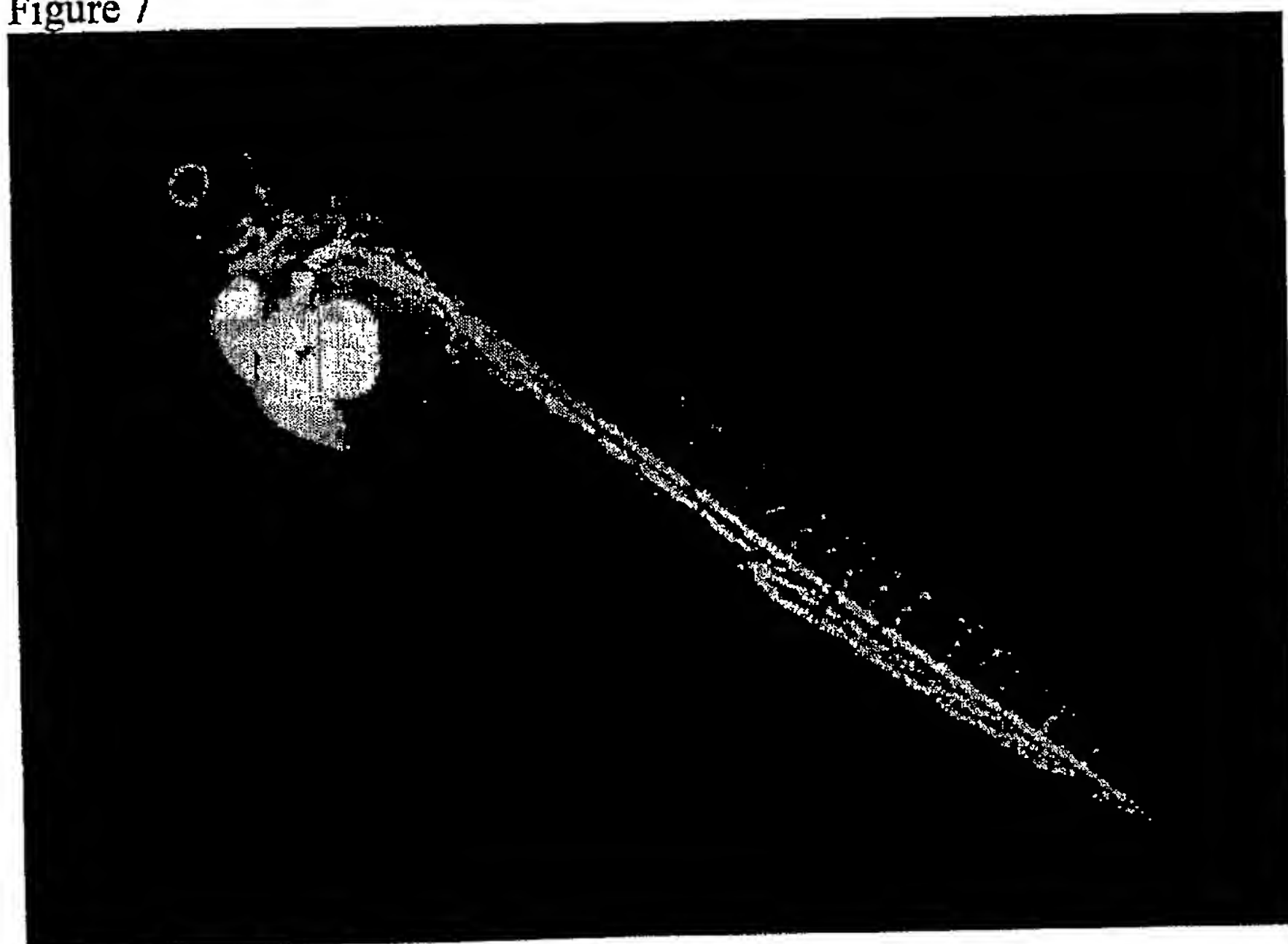


Figure 8



Figure 9

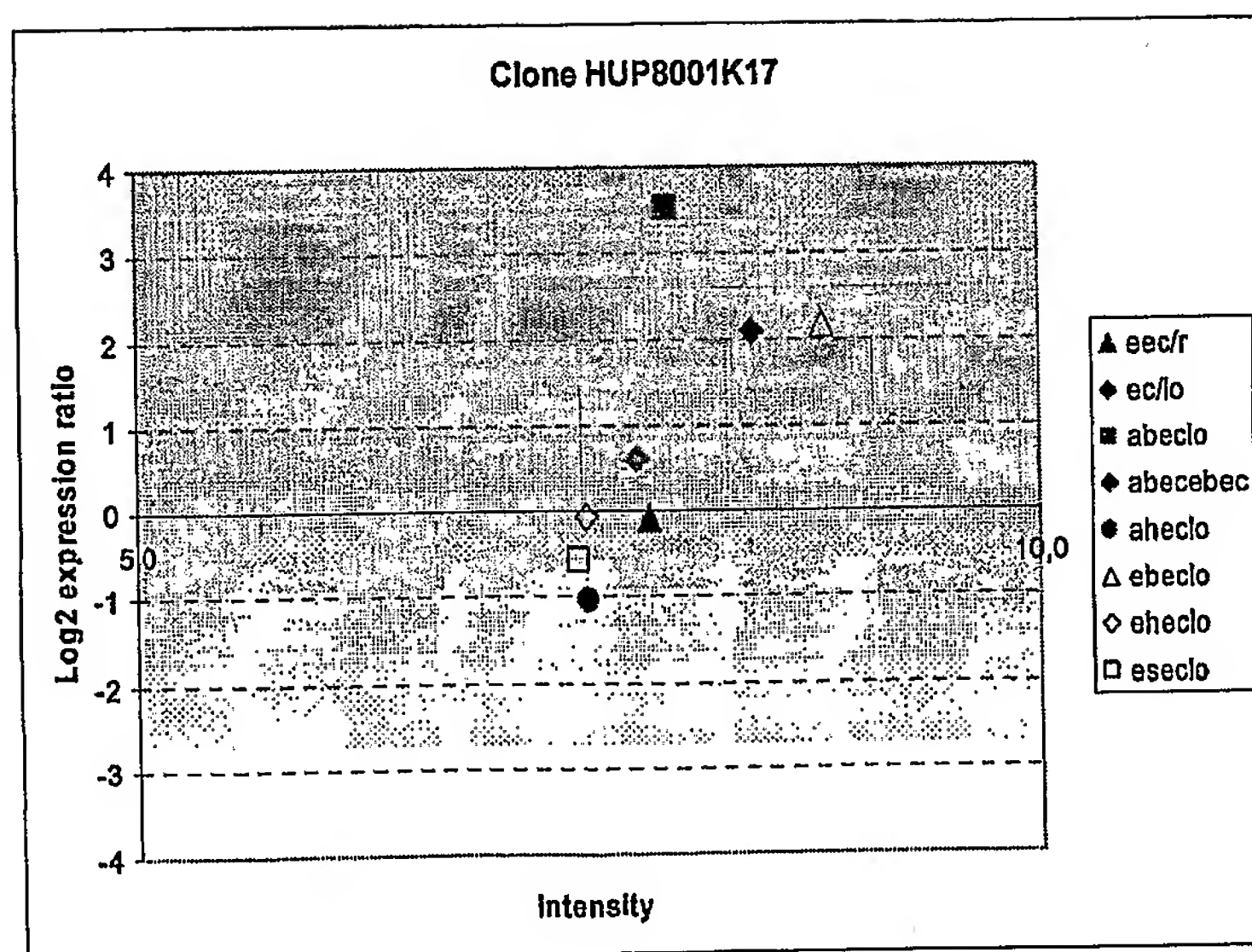


Figure 10



Figure 11

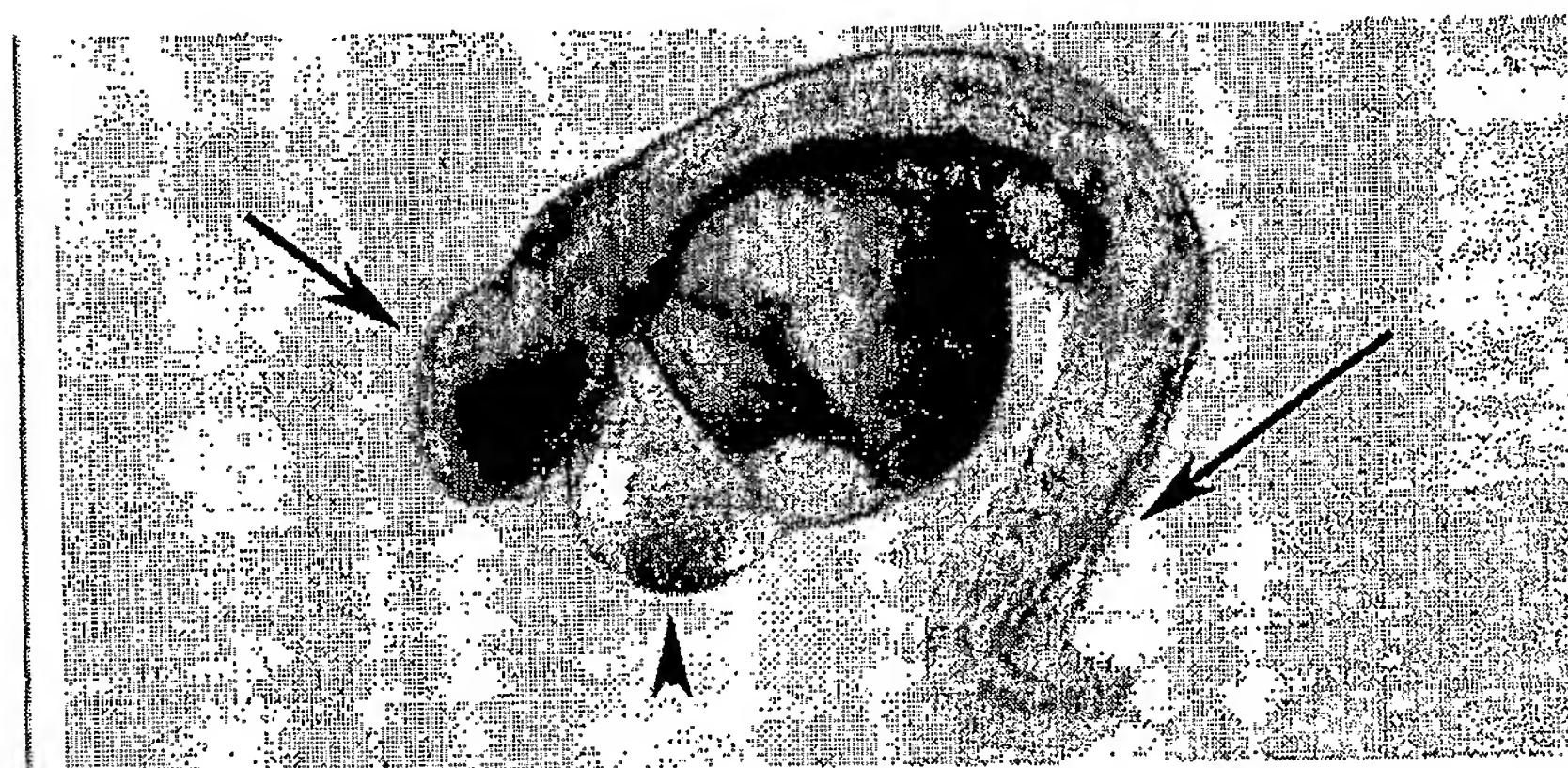


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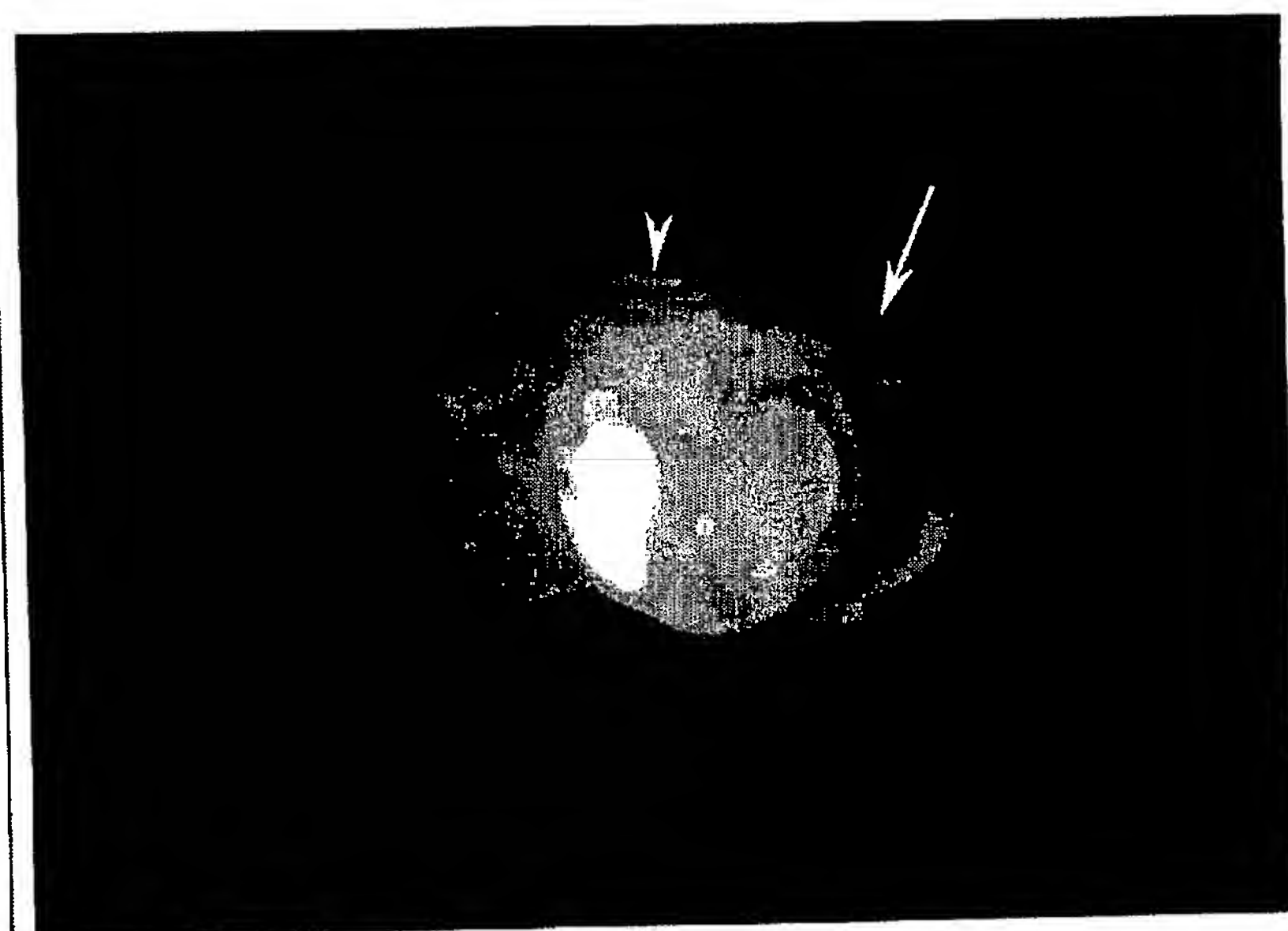


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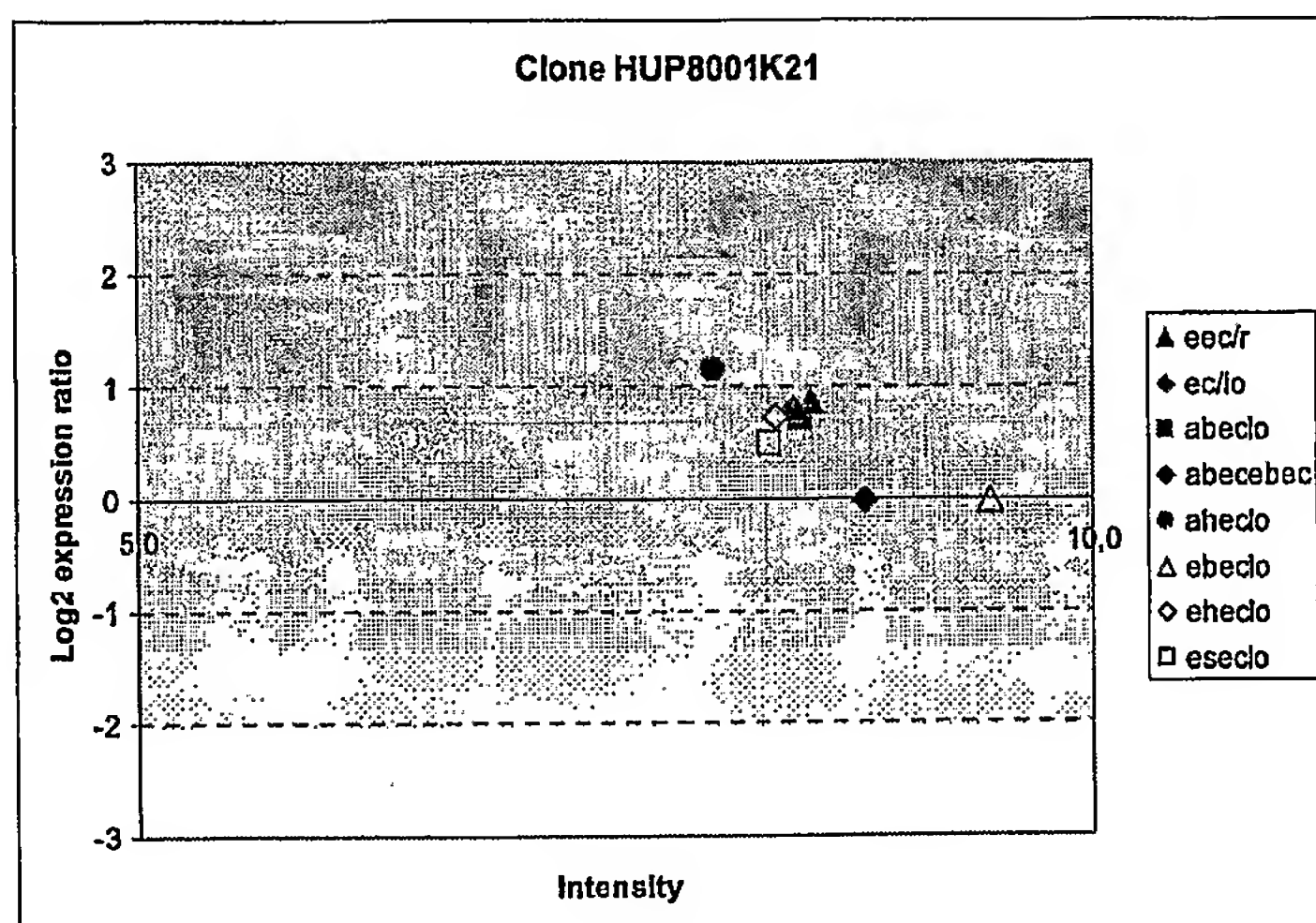


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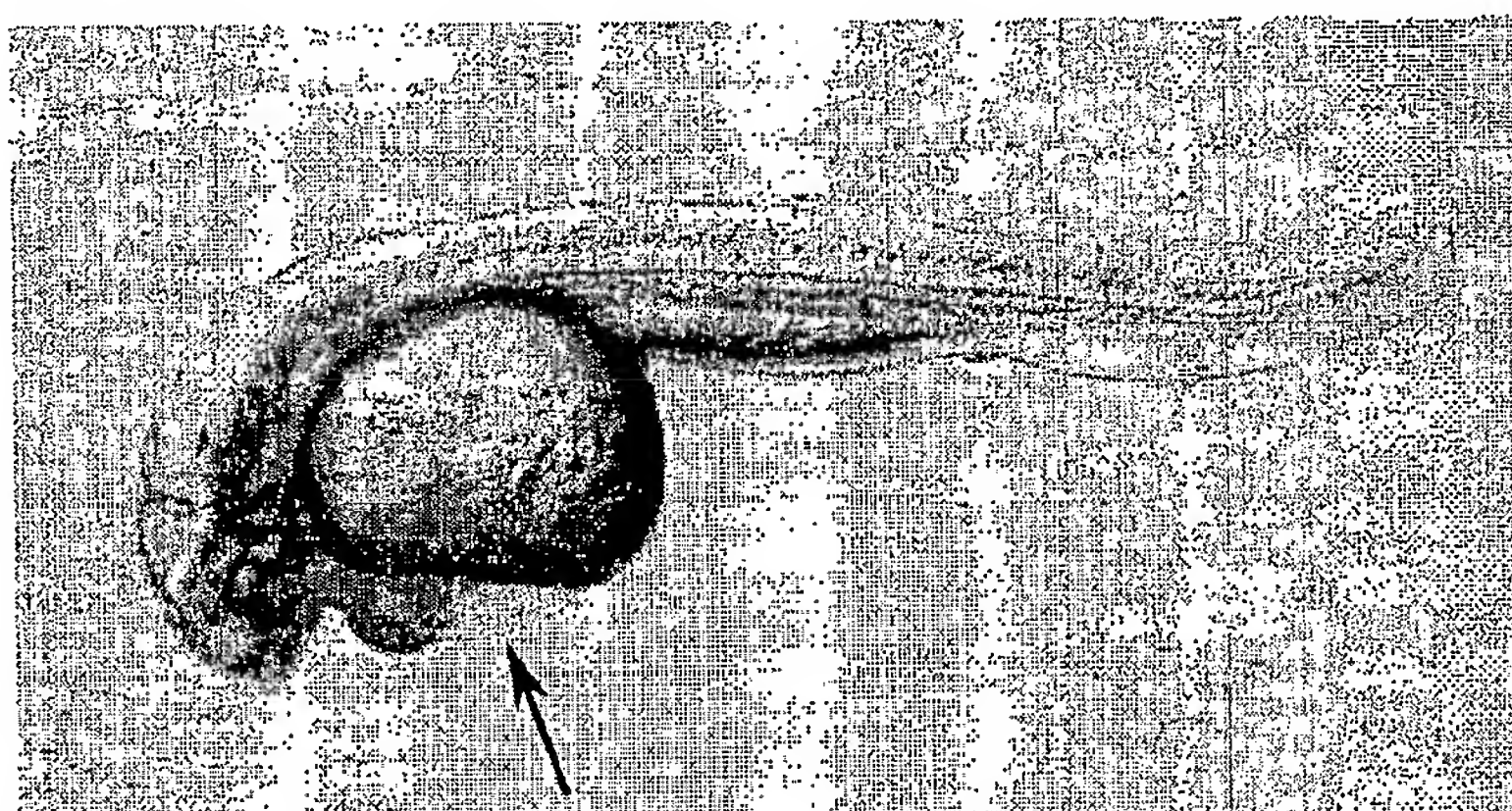


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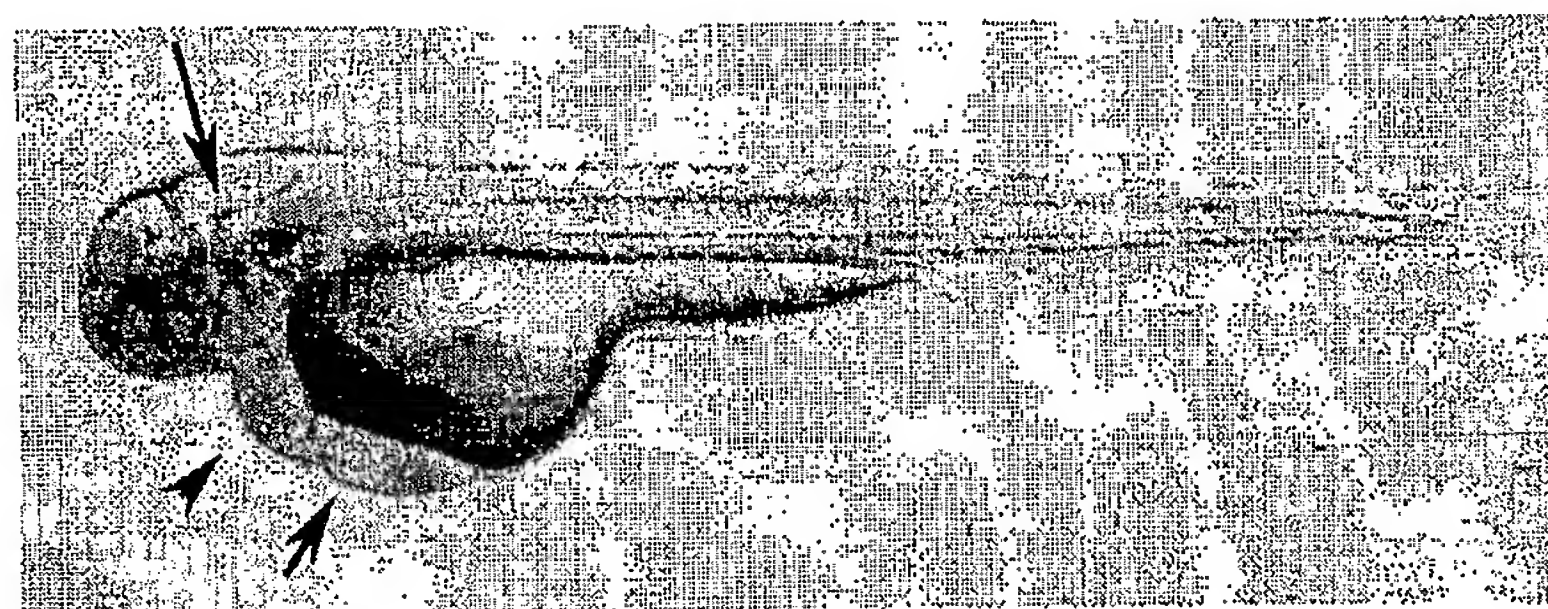


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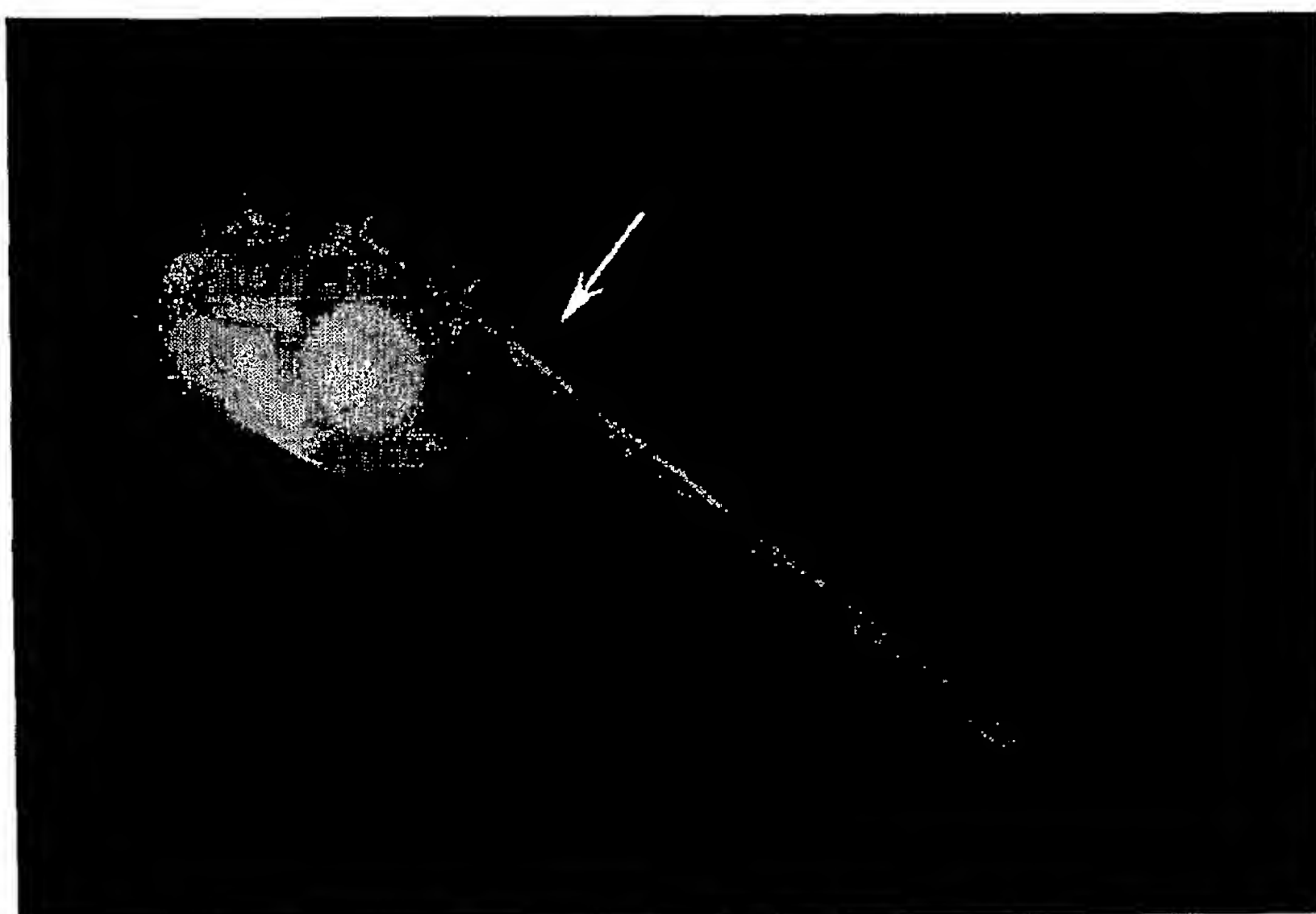


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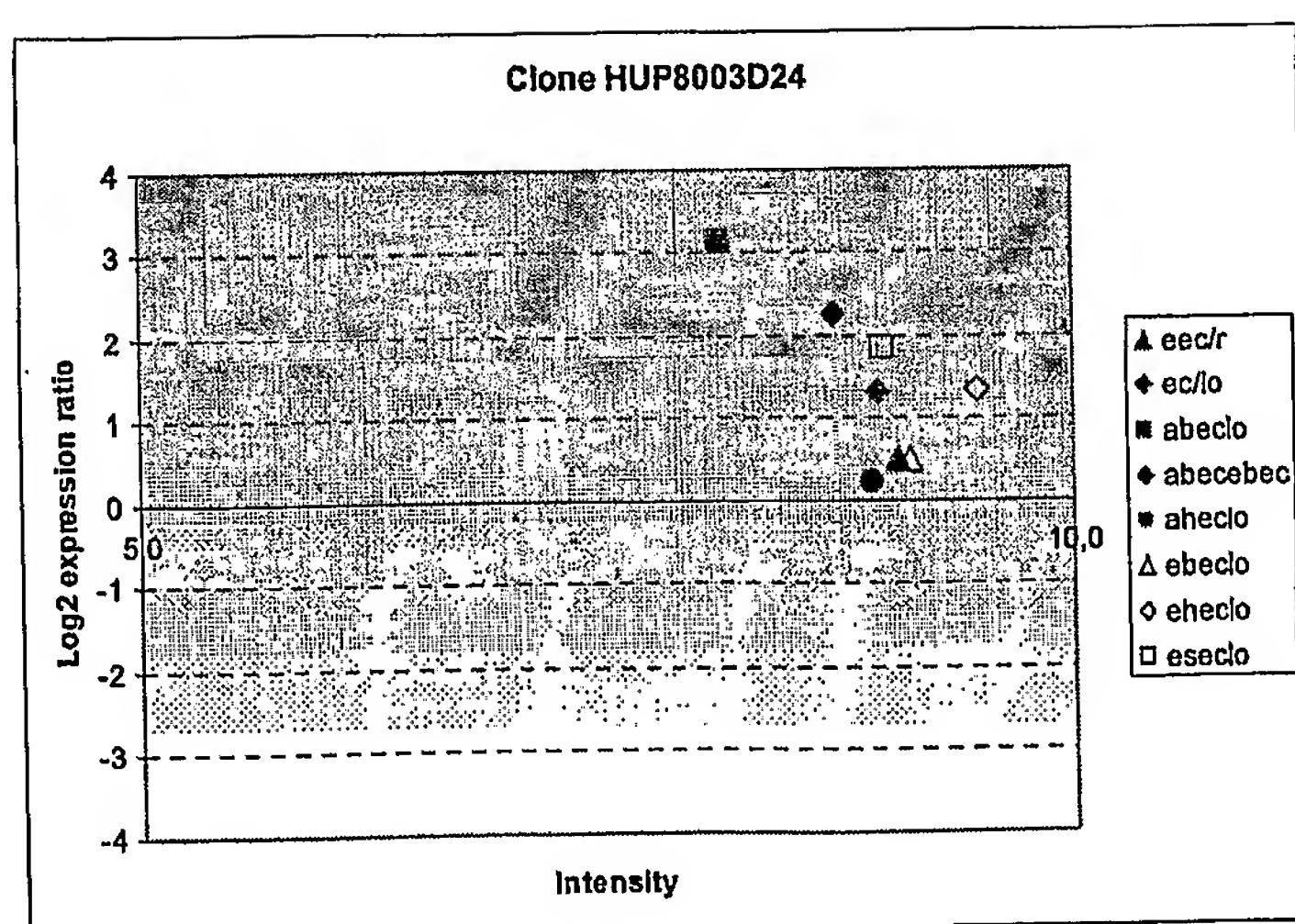


Figure 18



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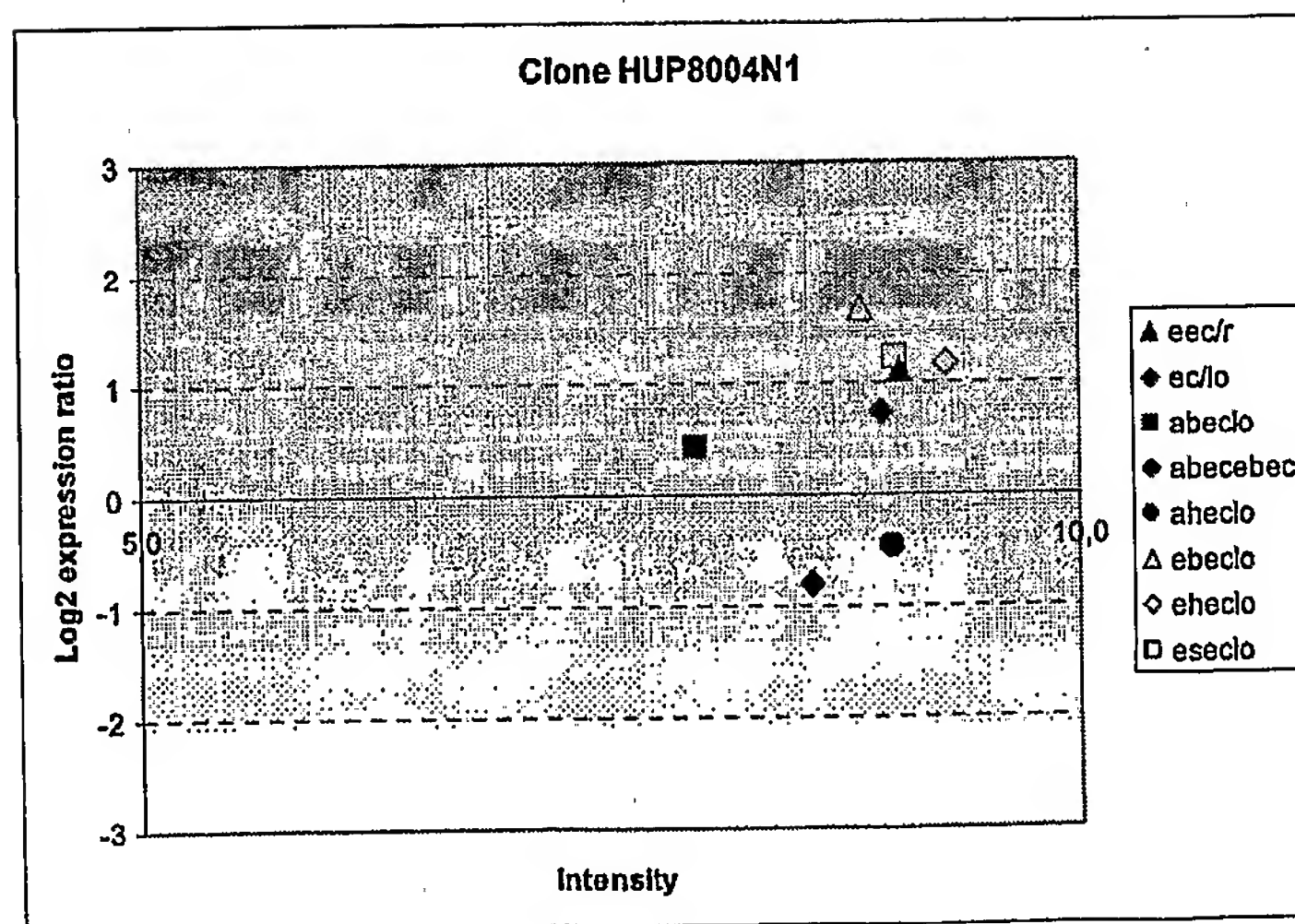


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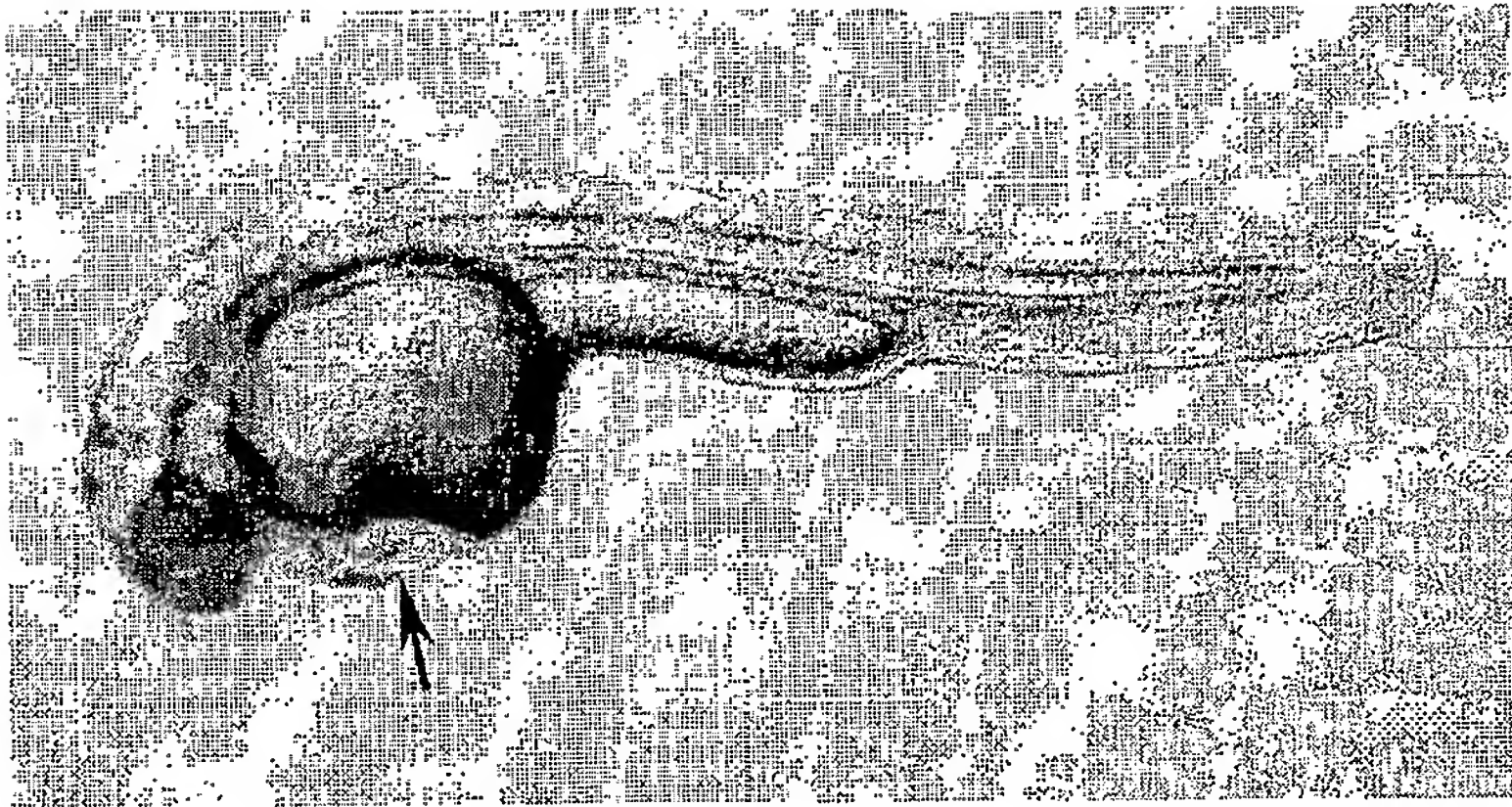


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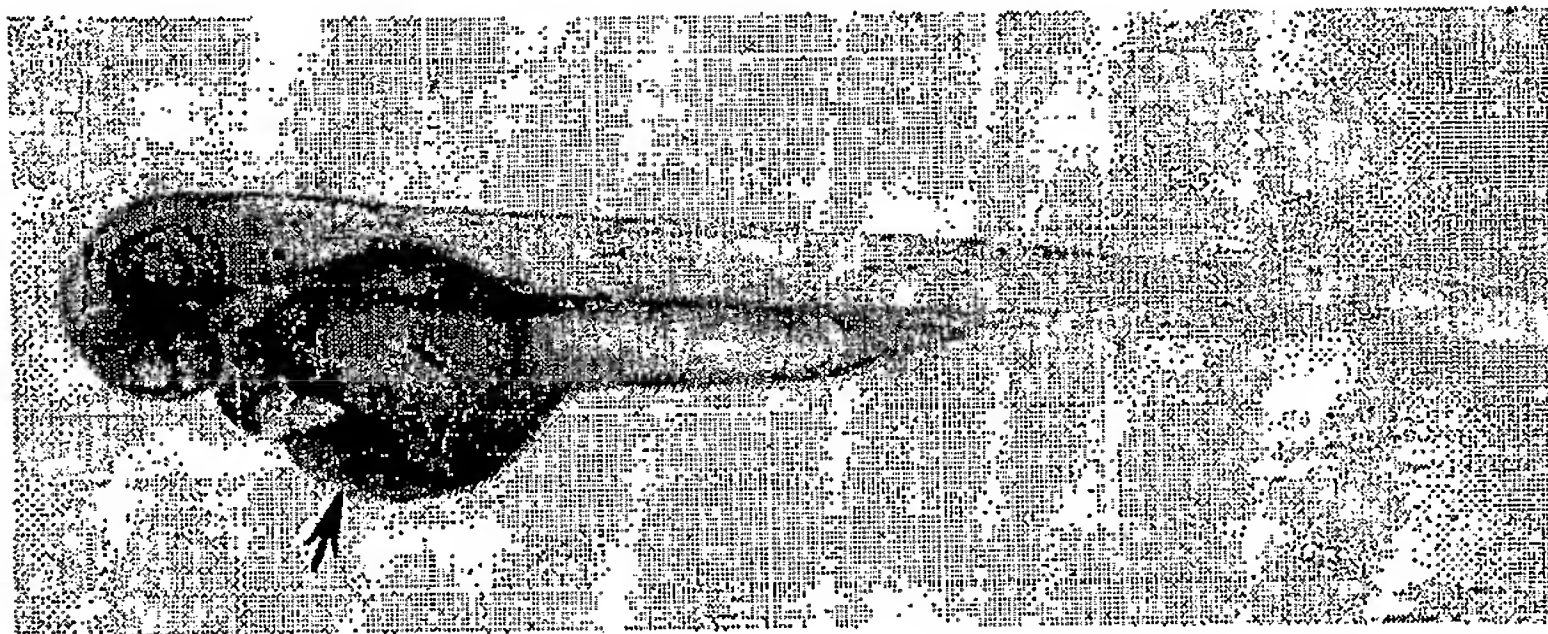


Figure 22



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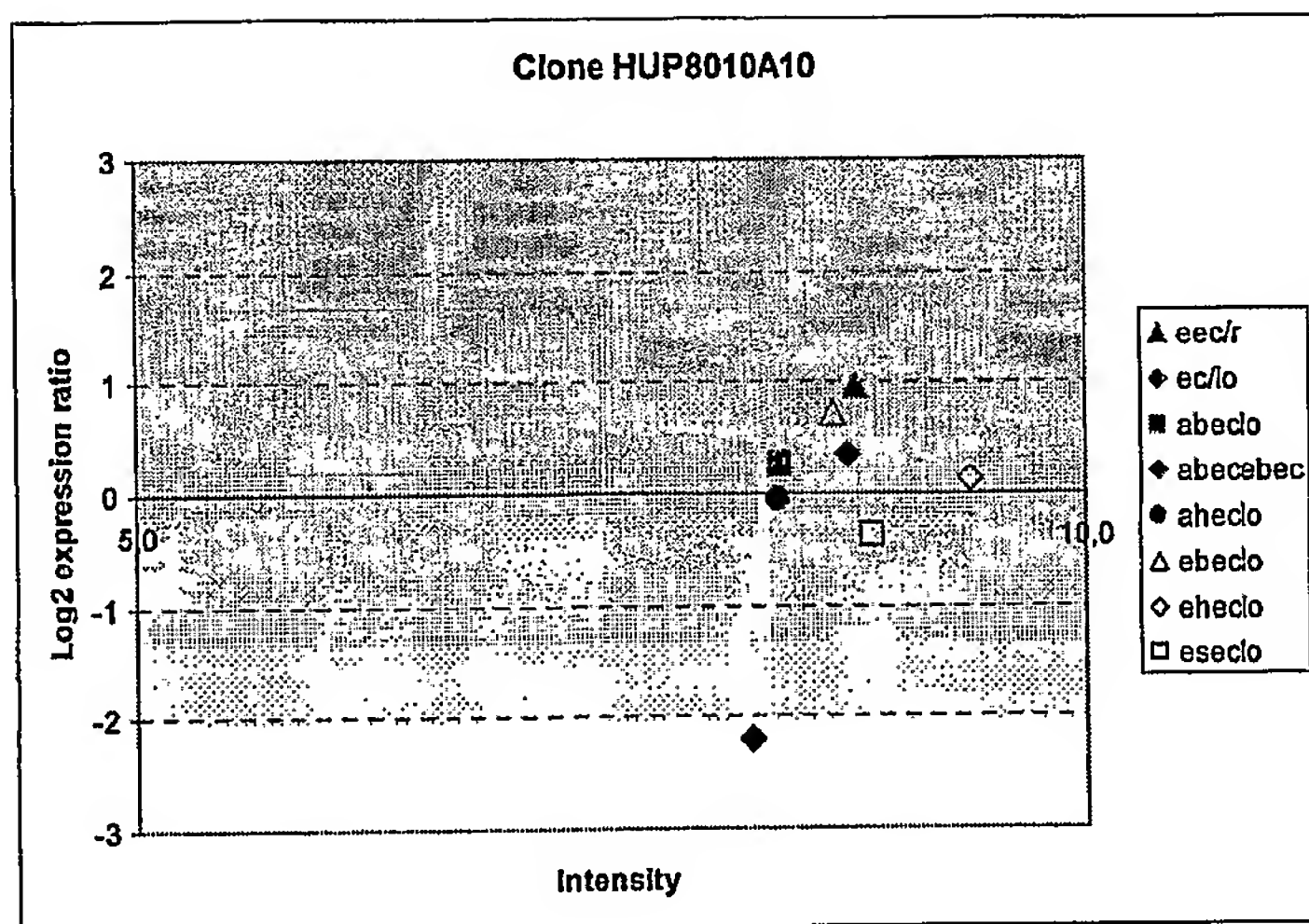


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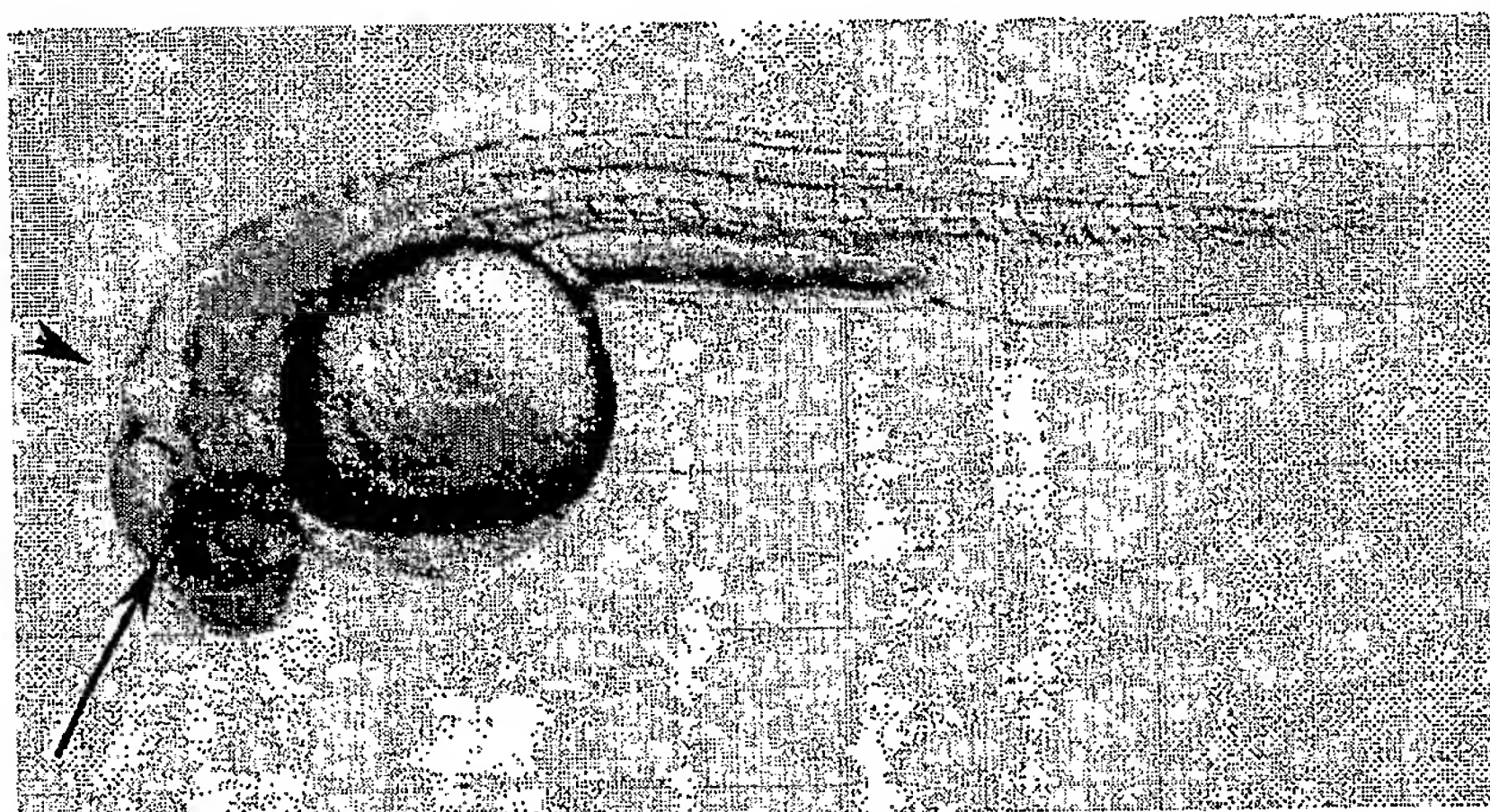


Figure 25



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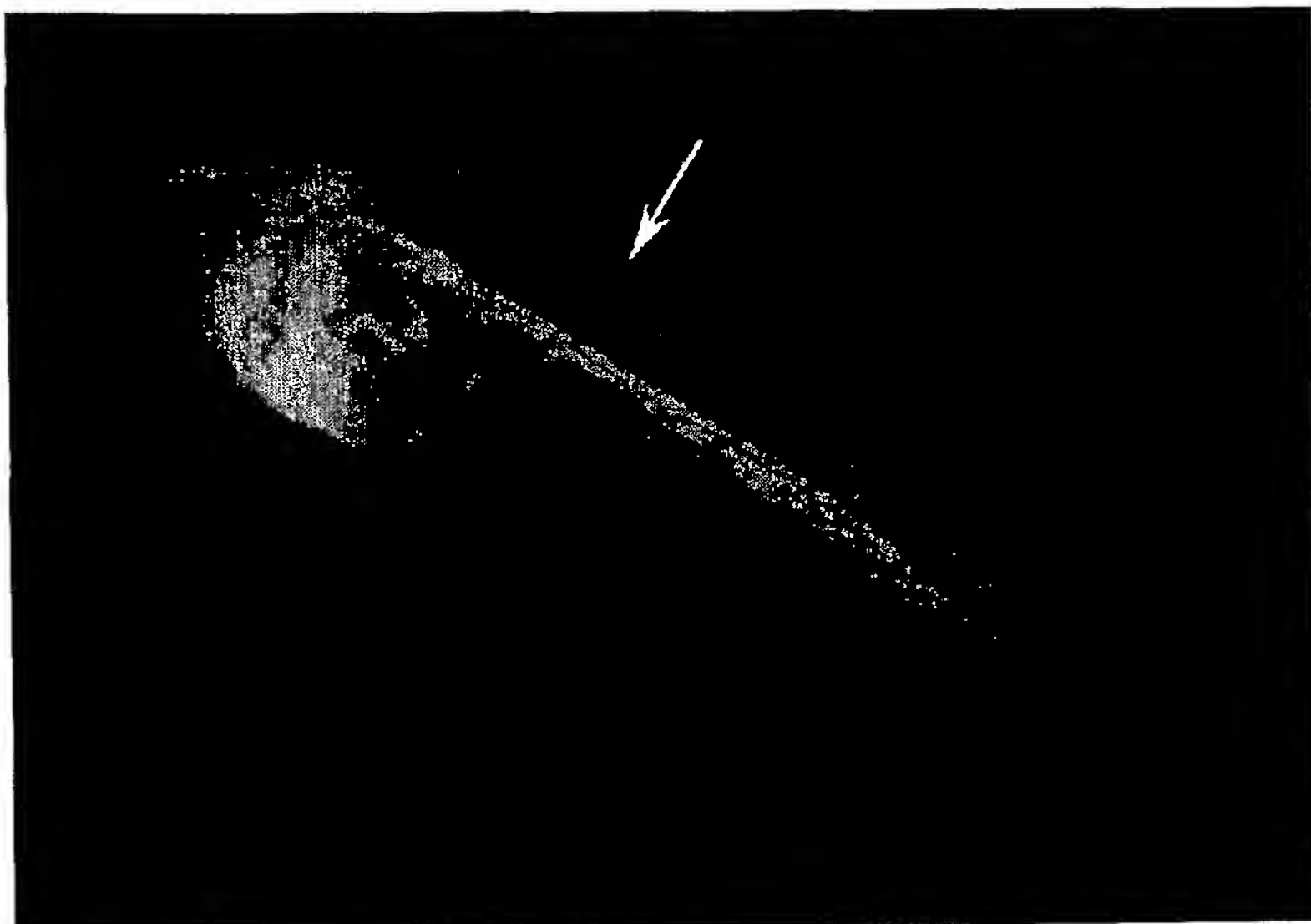


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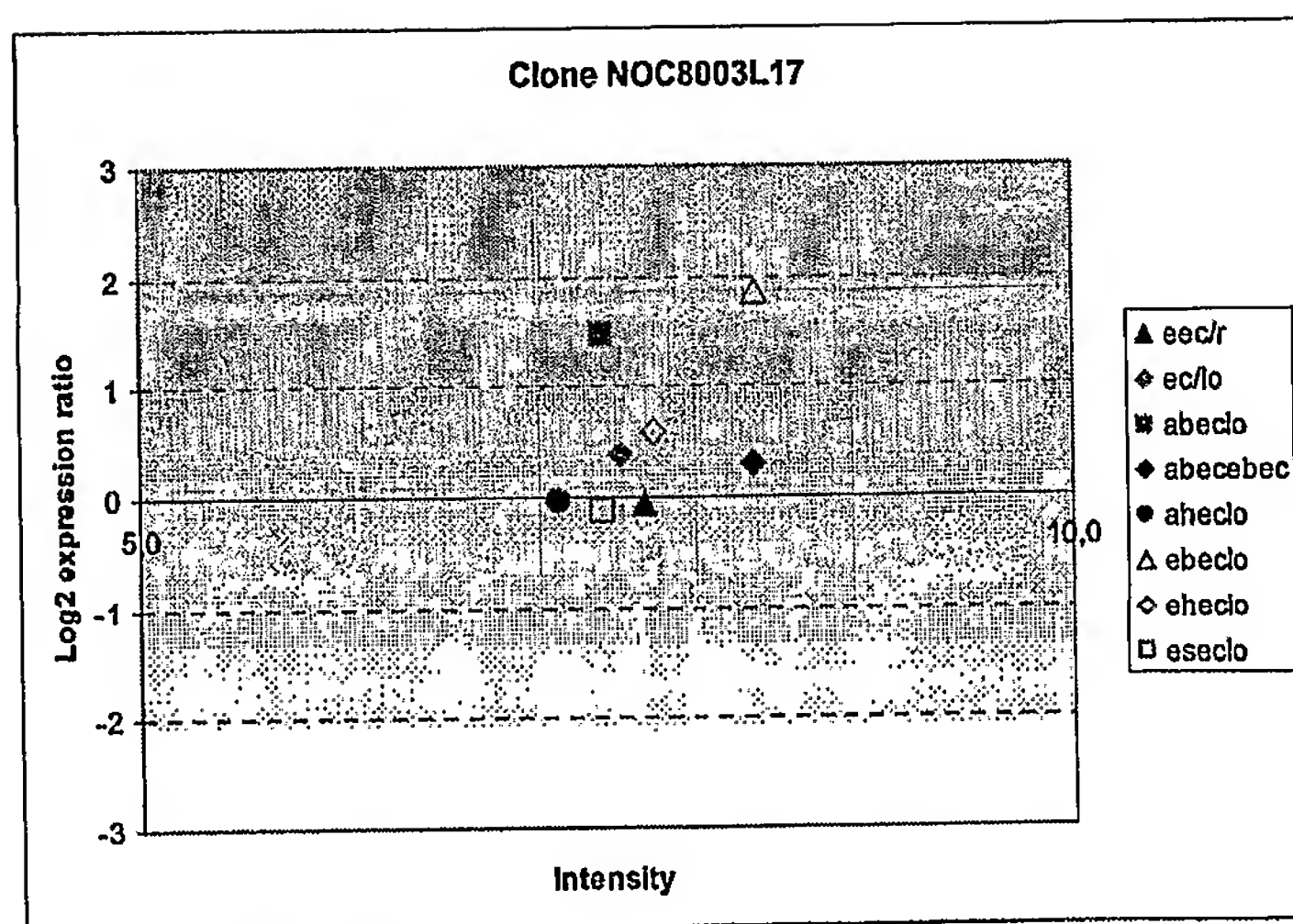


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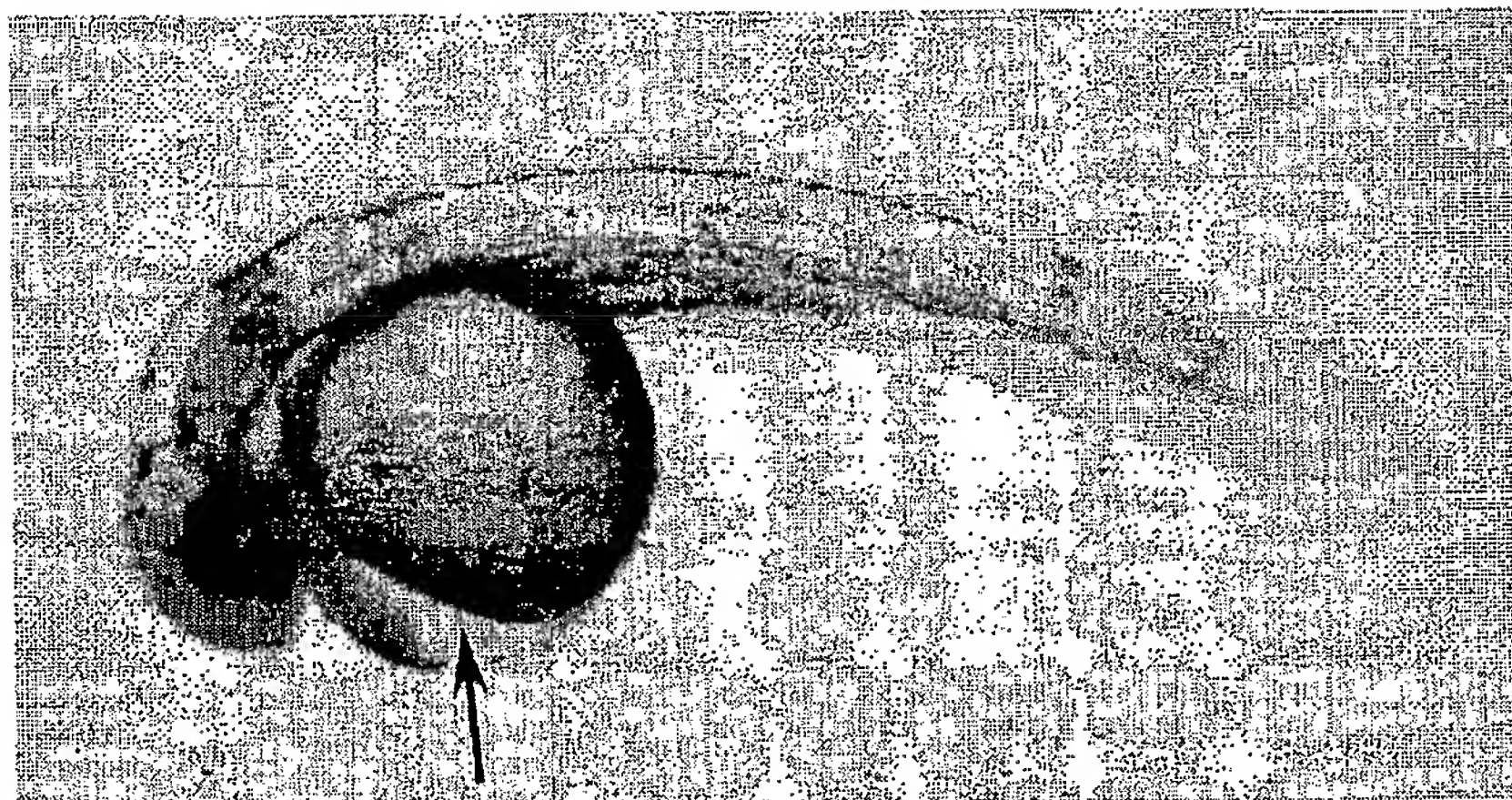


Figure 29



Figure 30



Figure 31

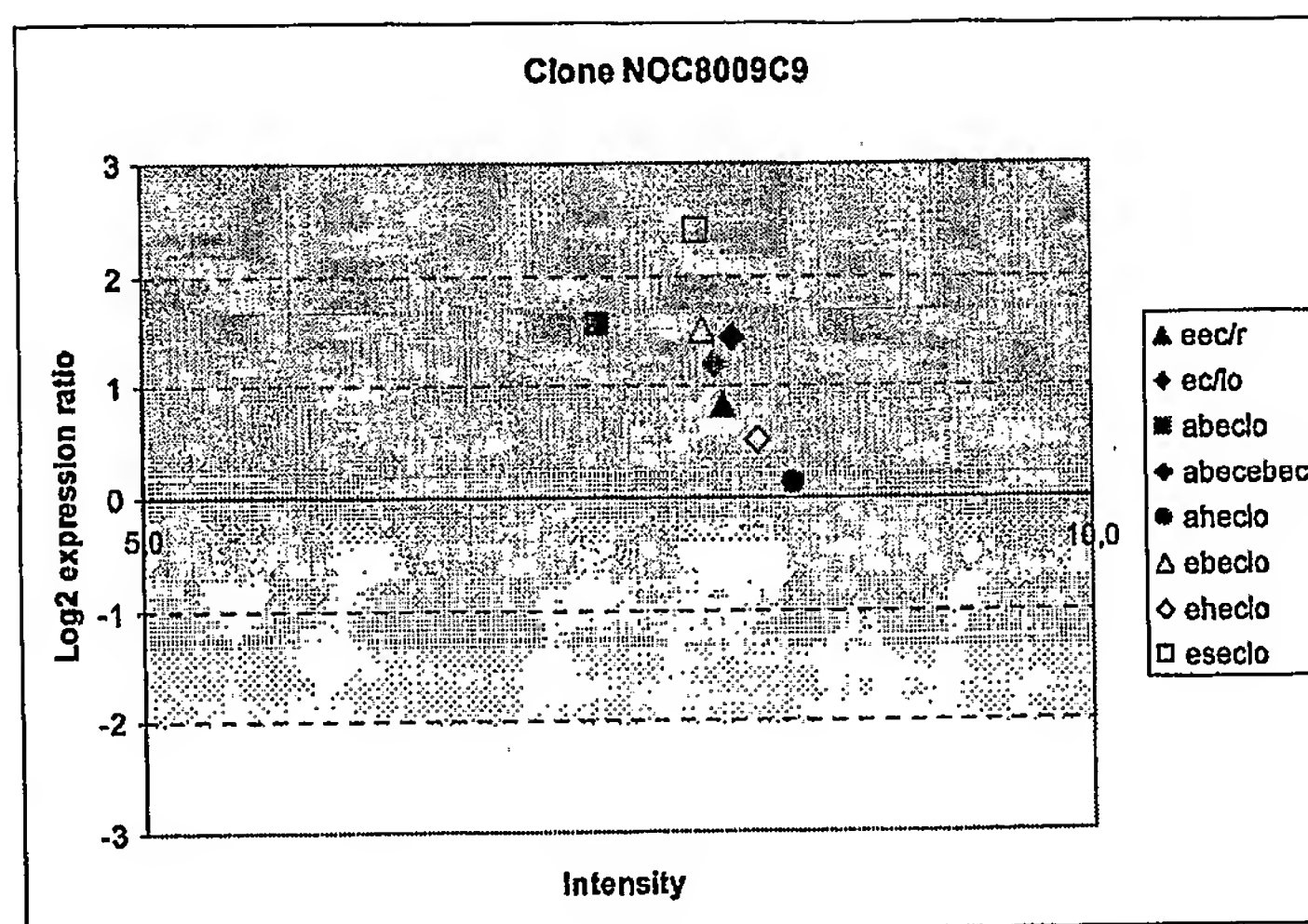


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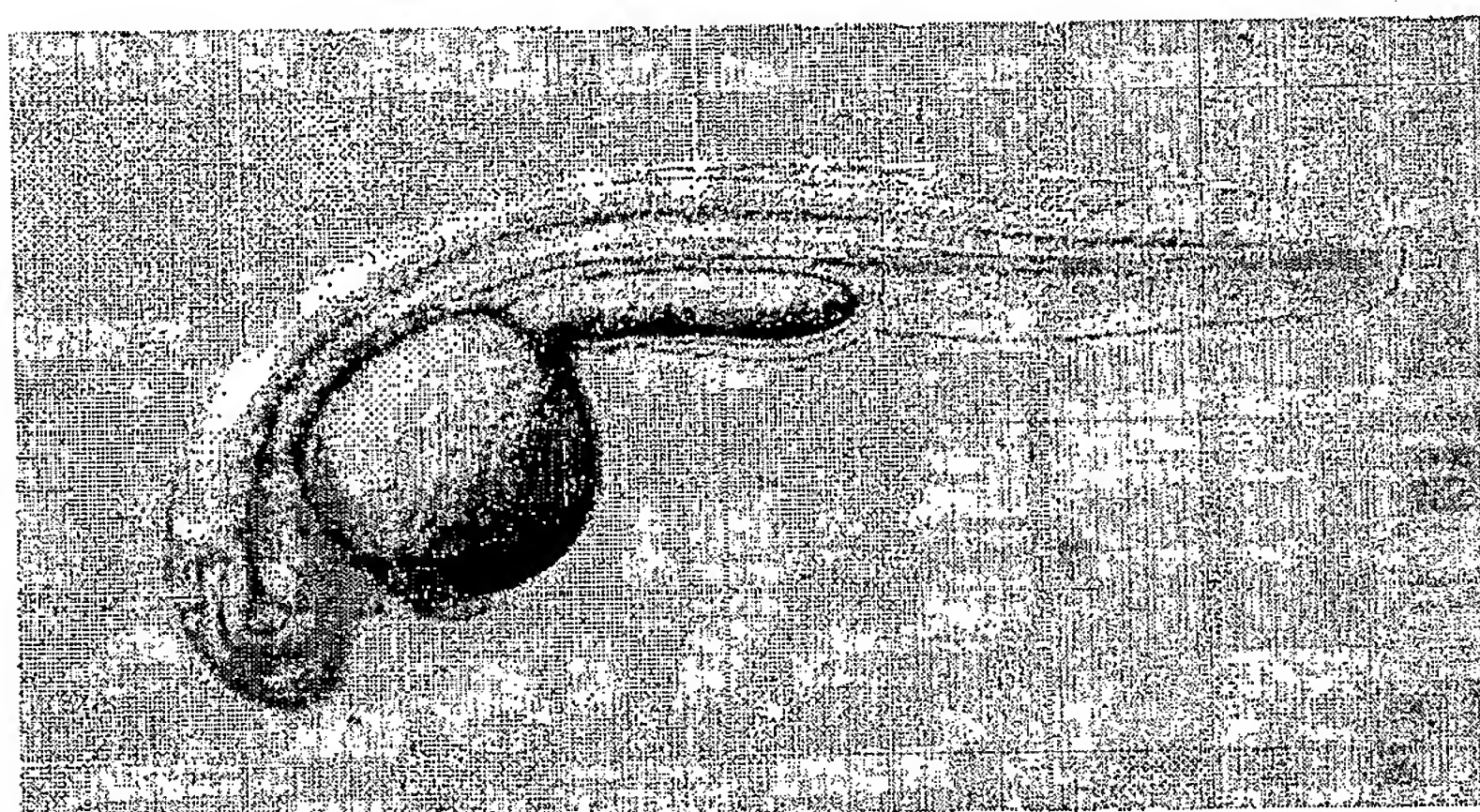


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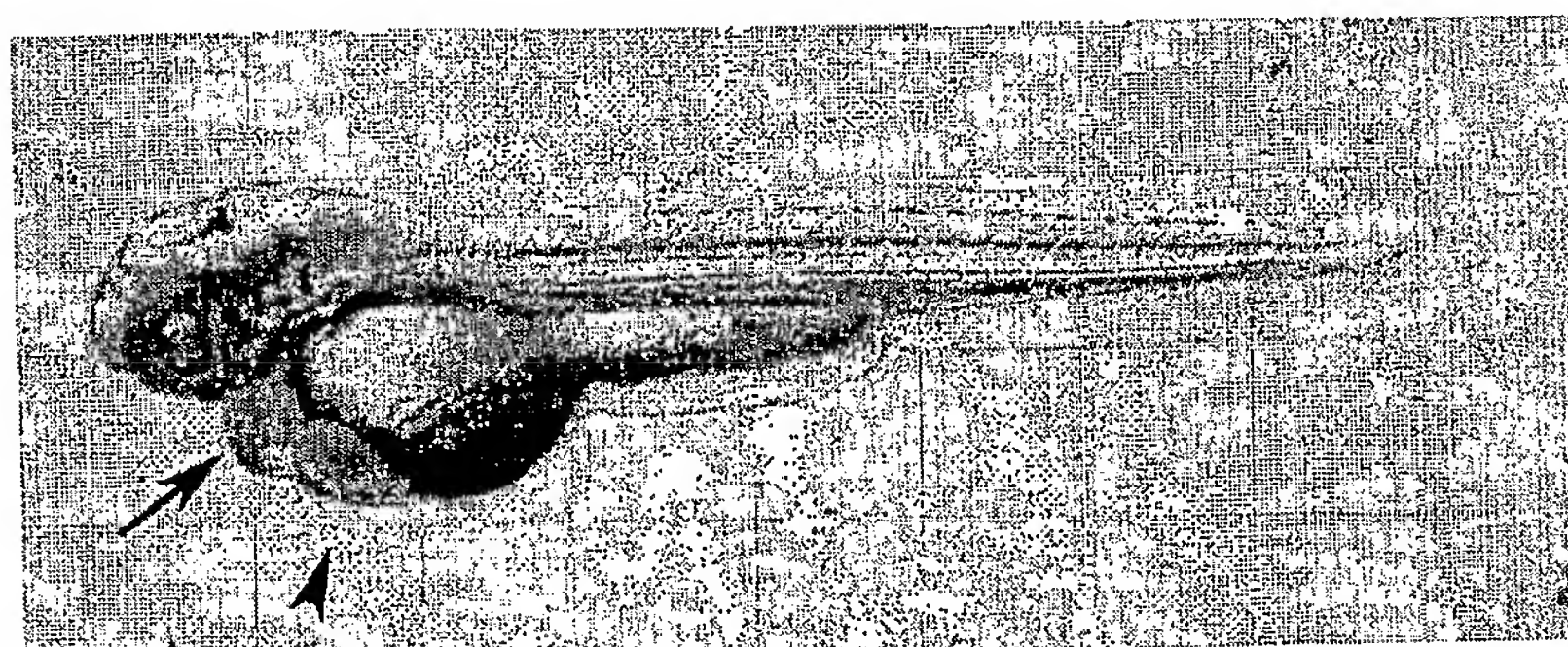


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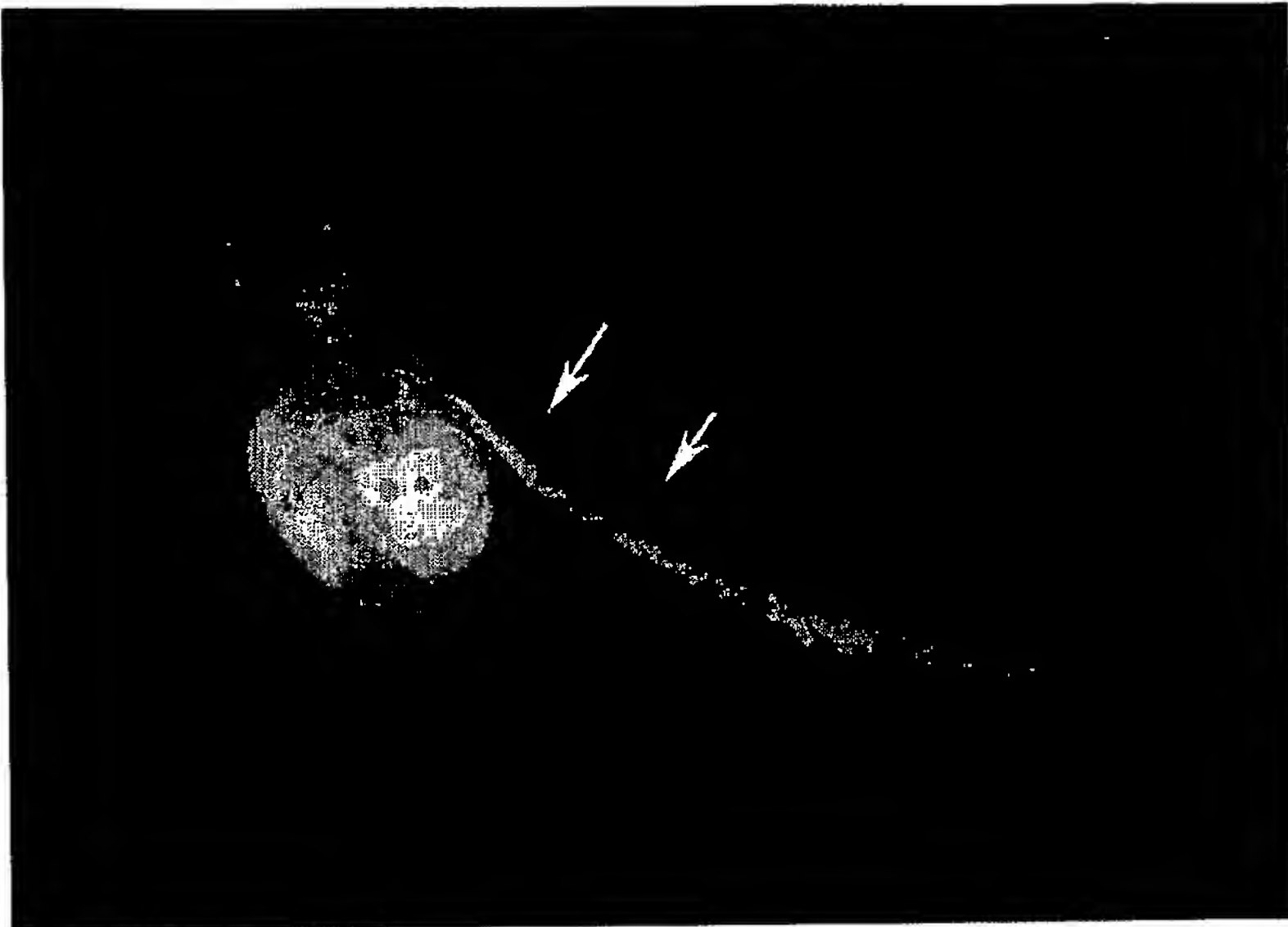


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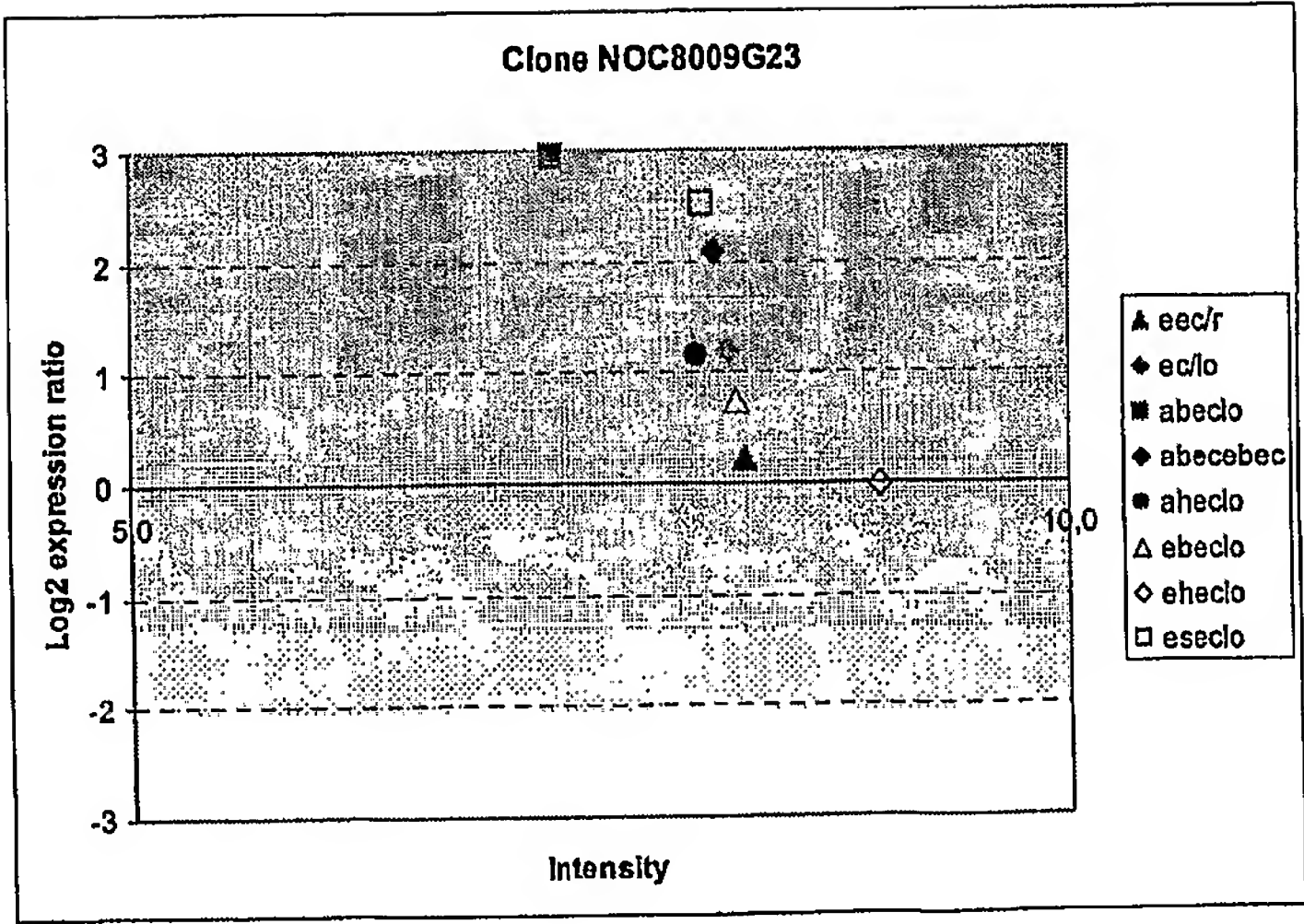


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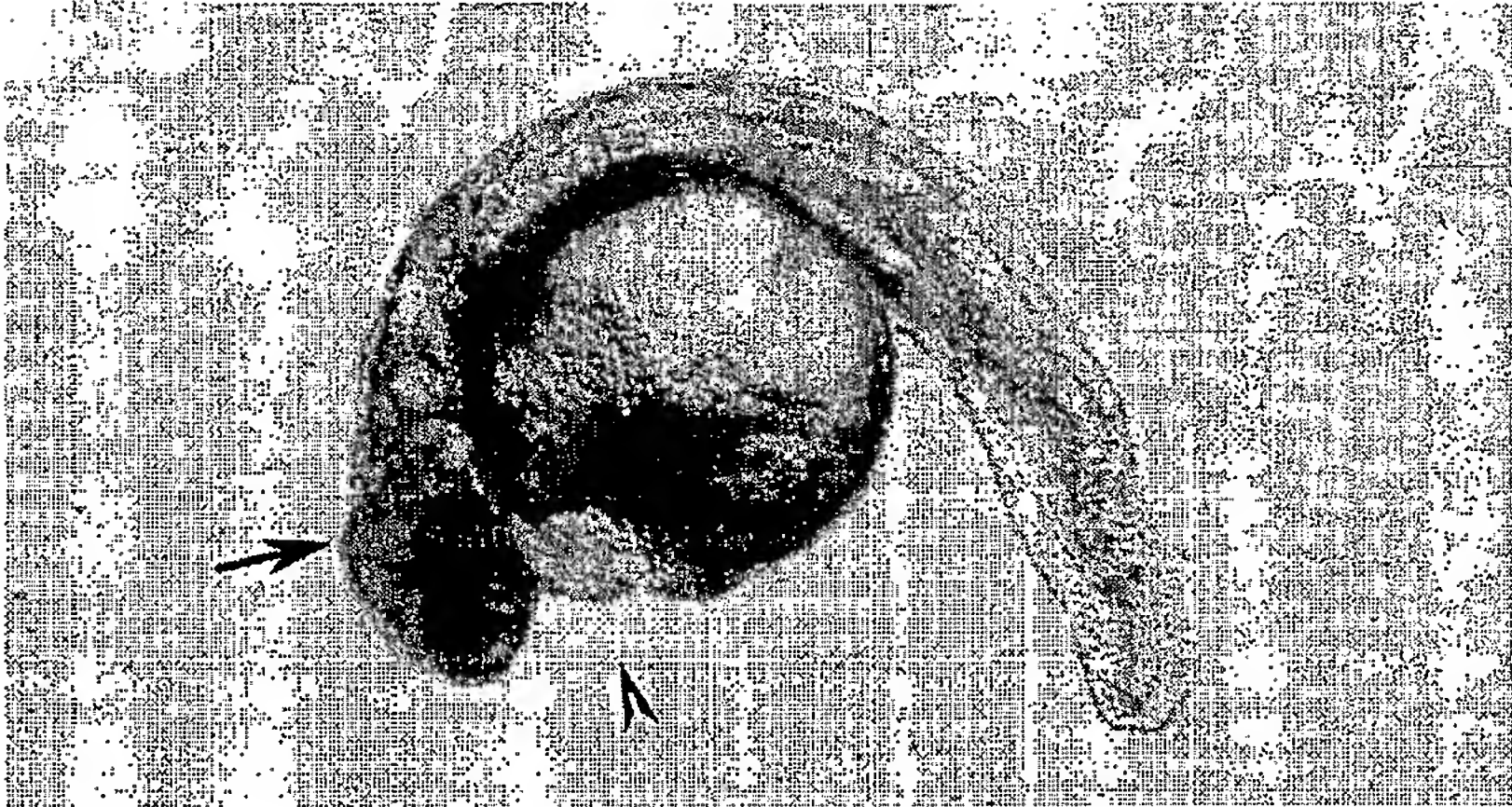


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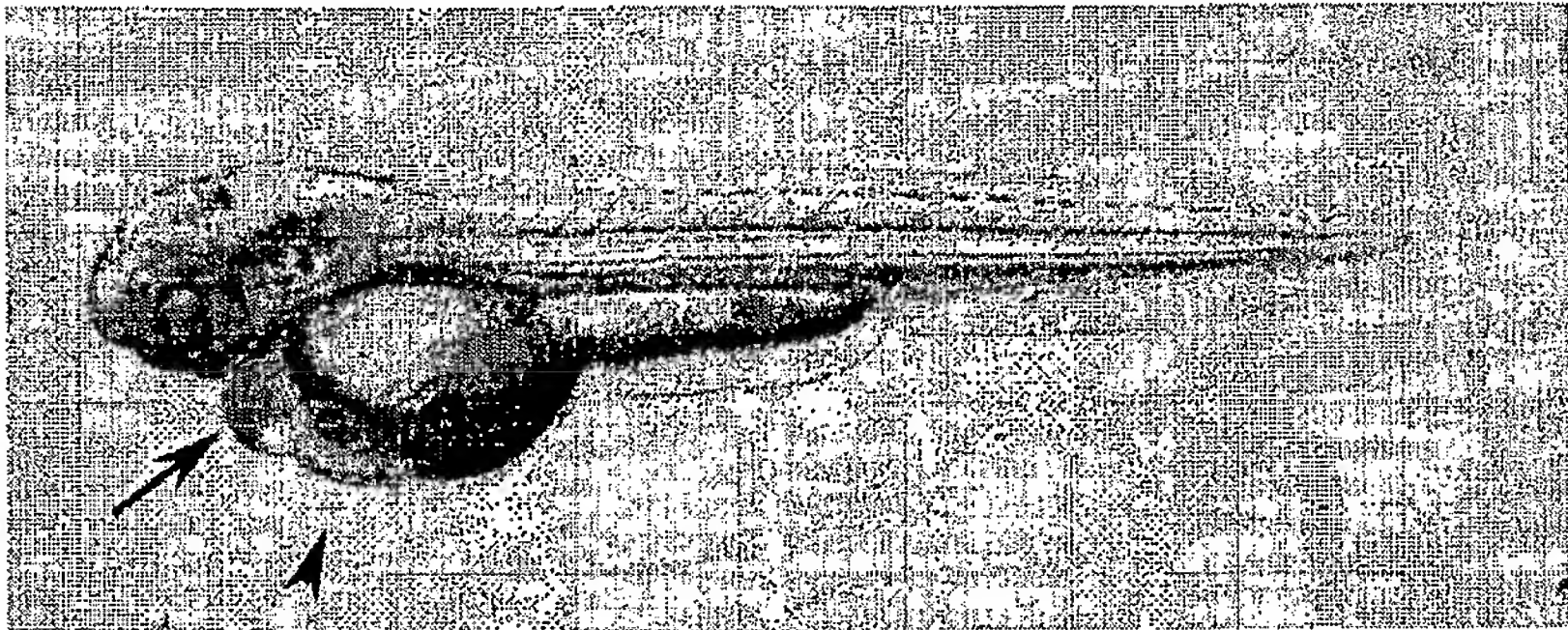


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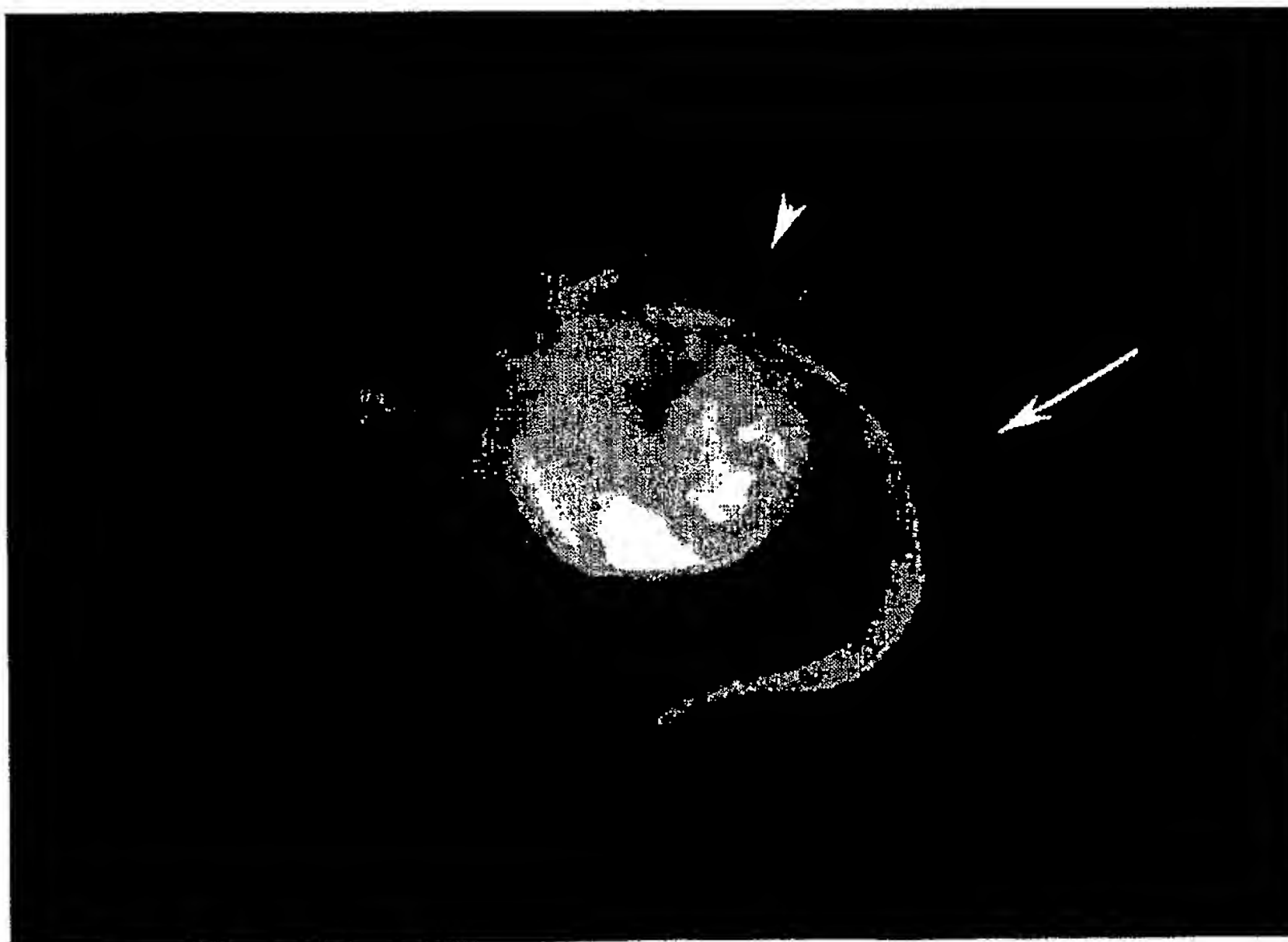


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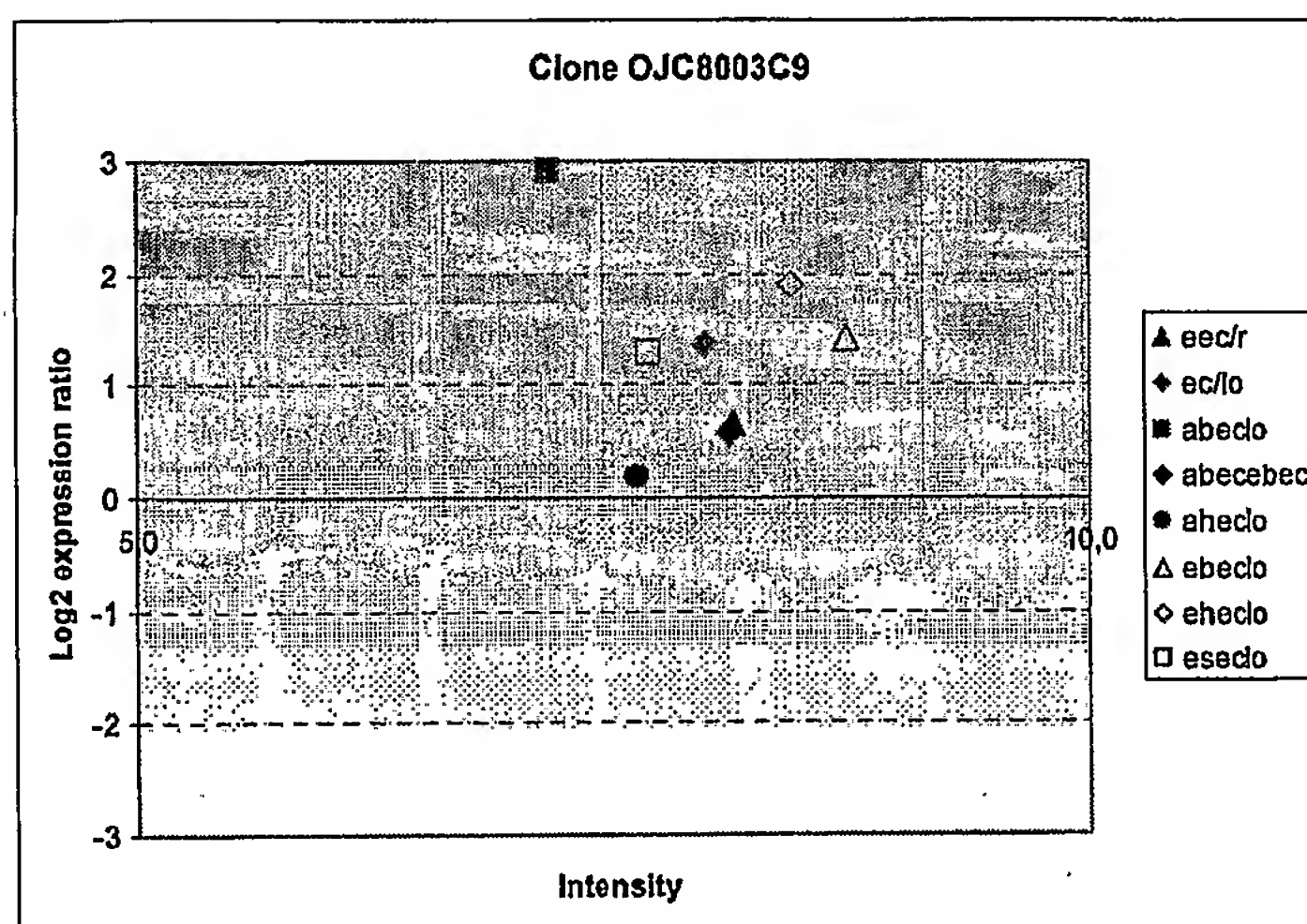


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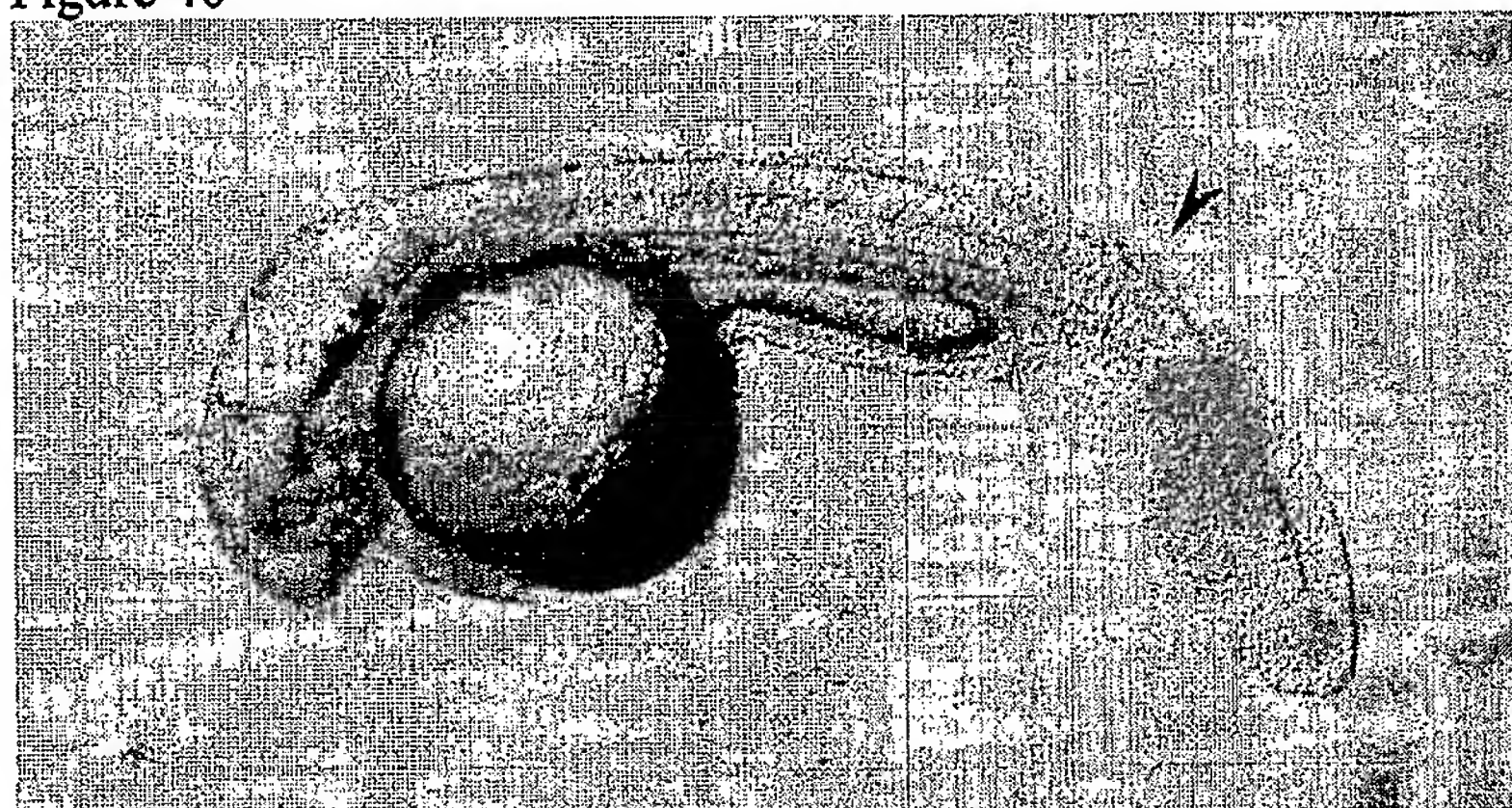


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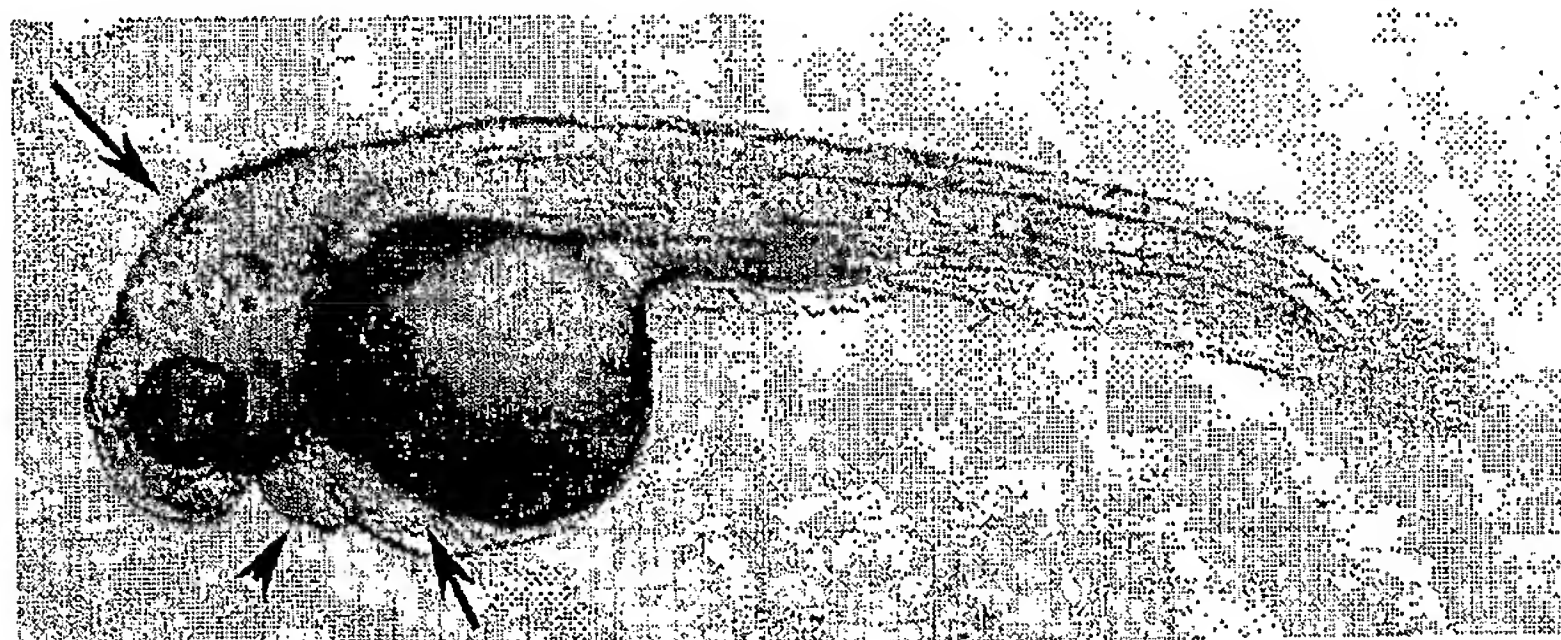


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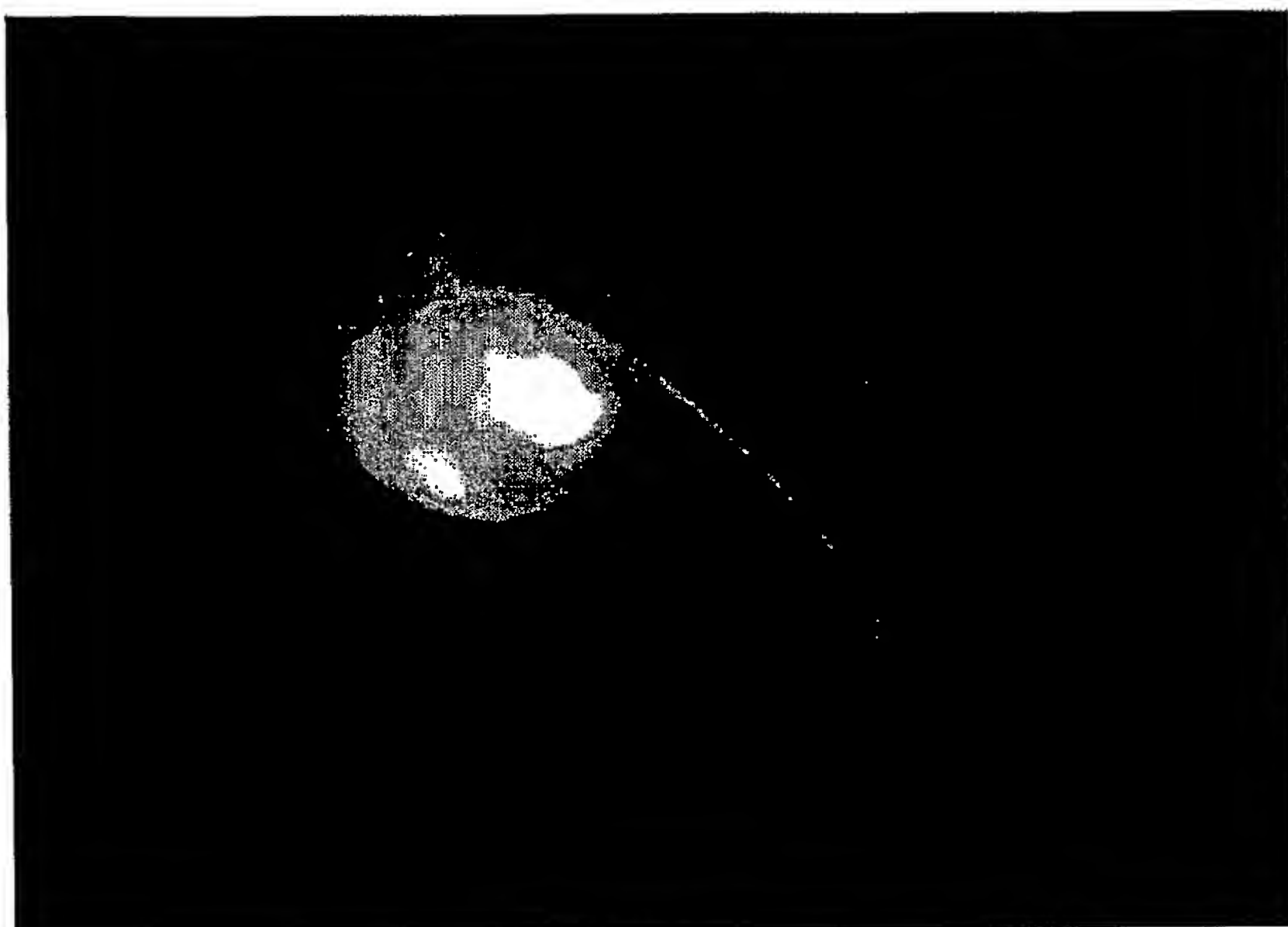


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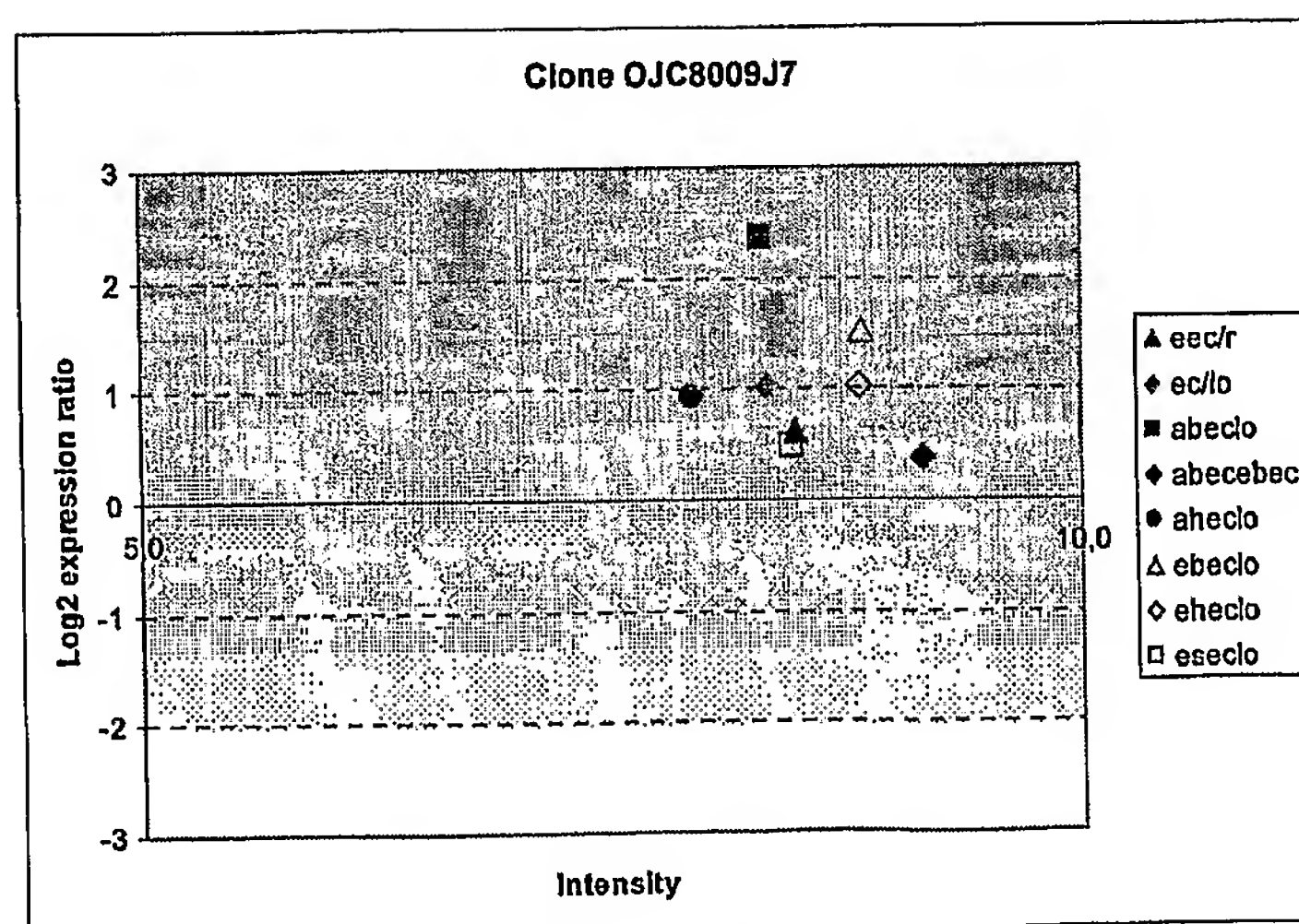


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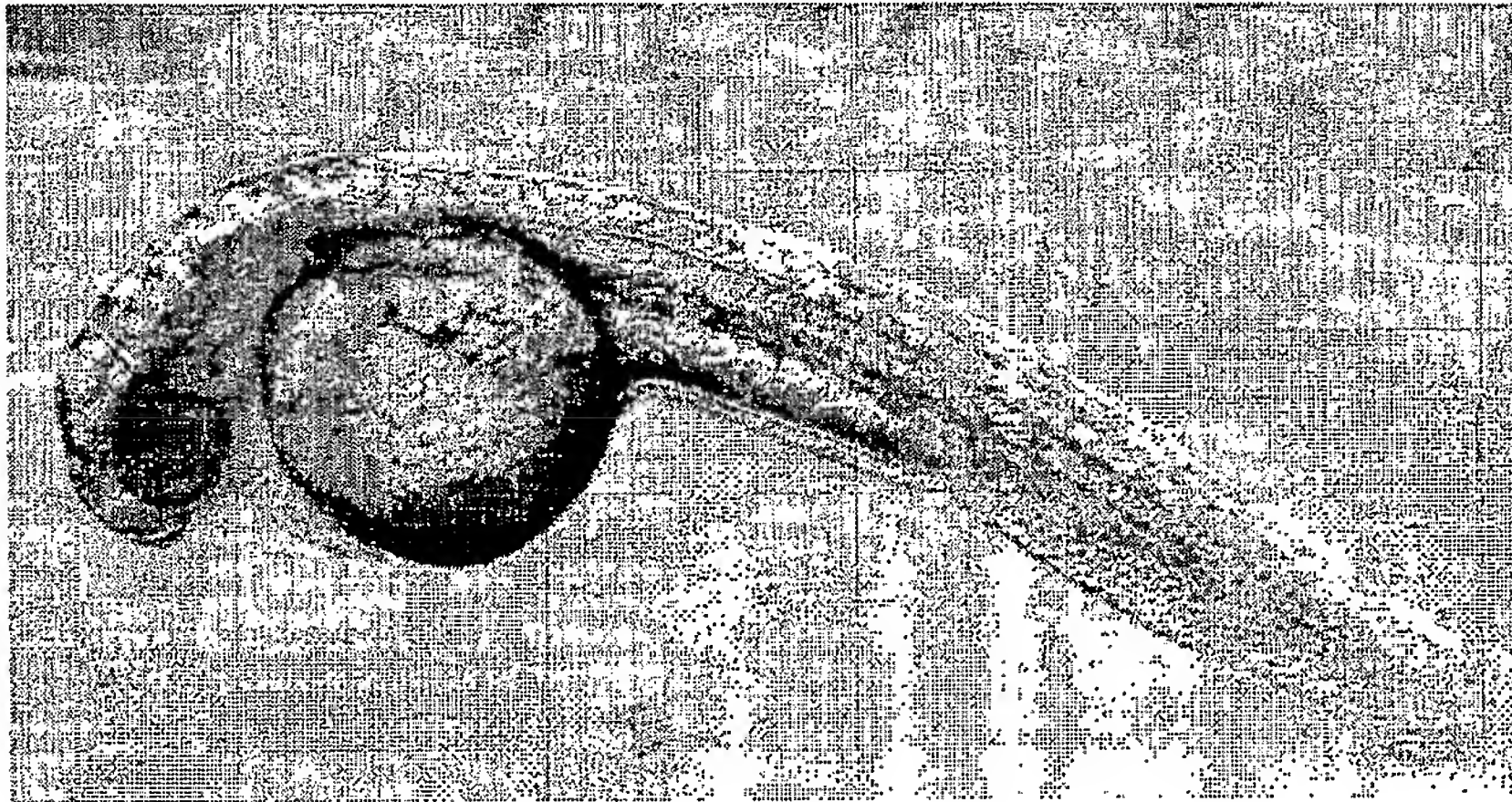


Figure 45

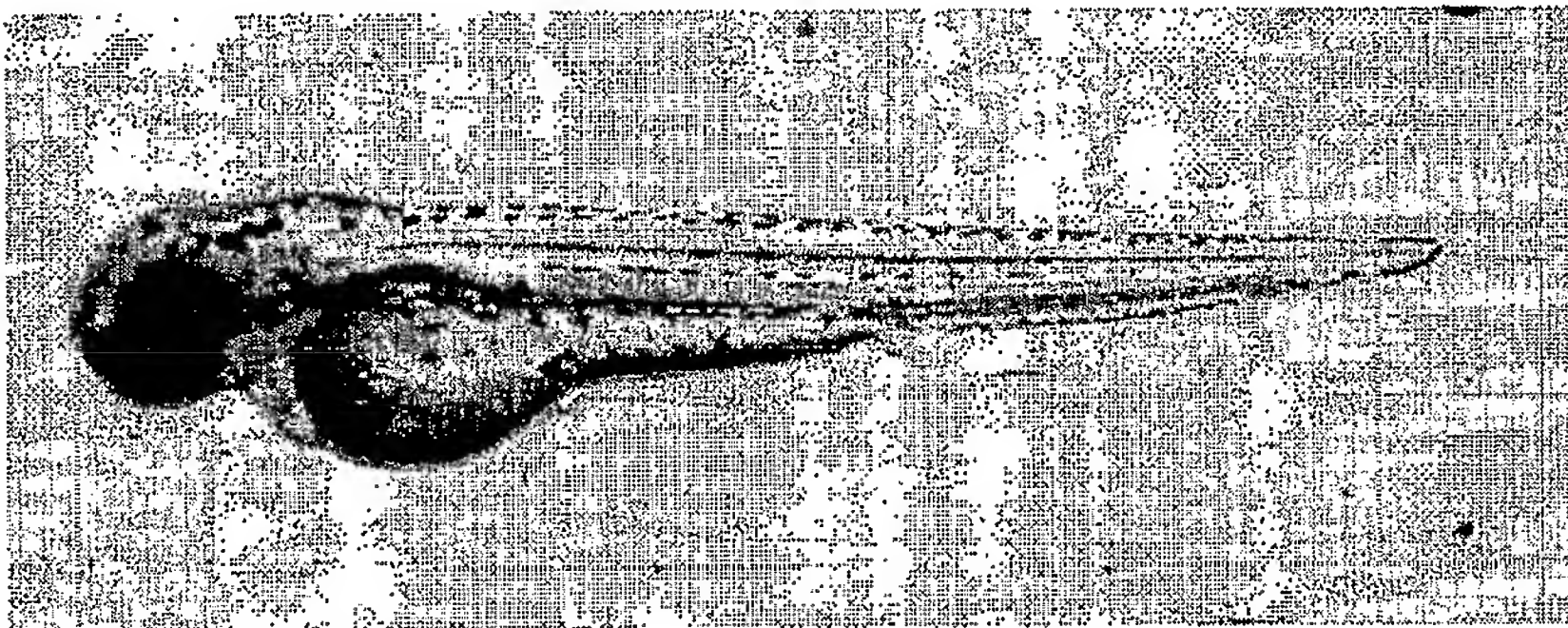


Figure 46

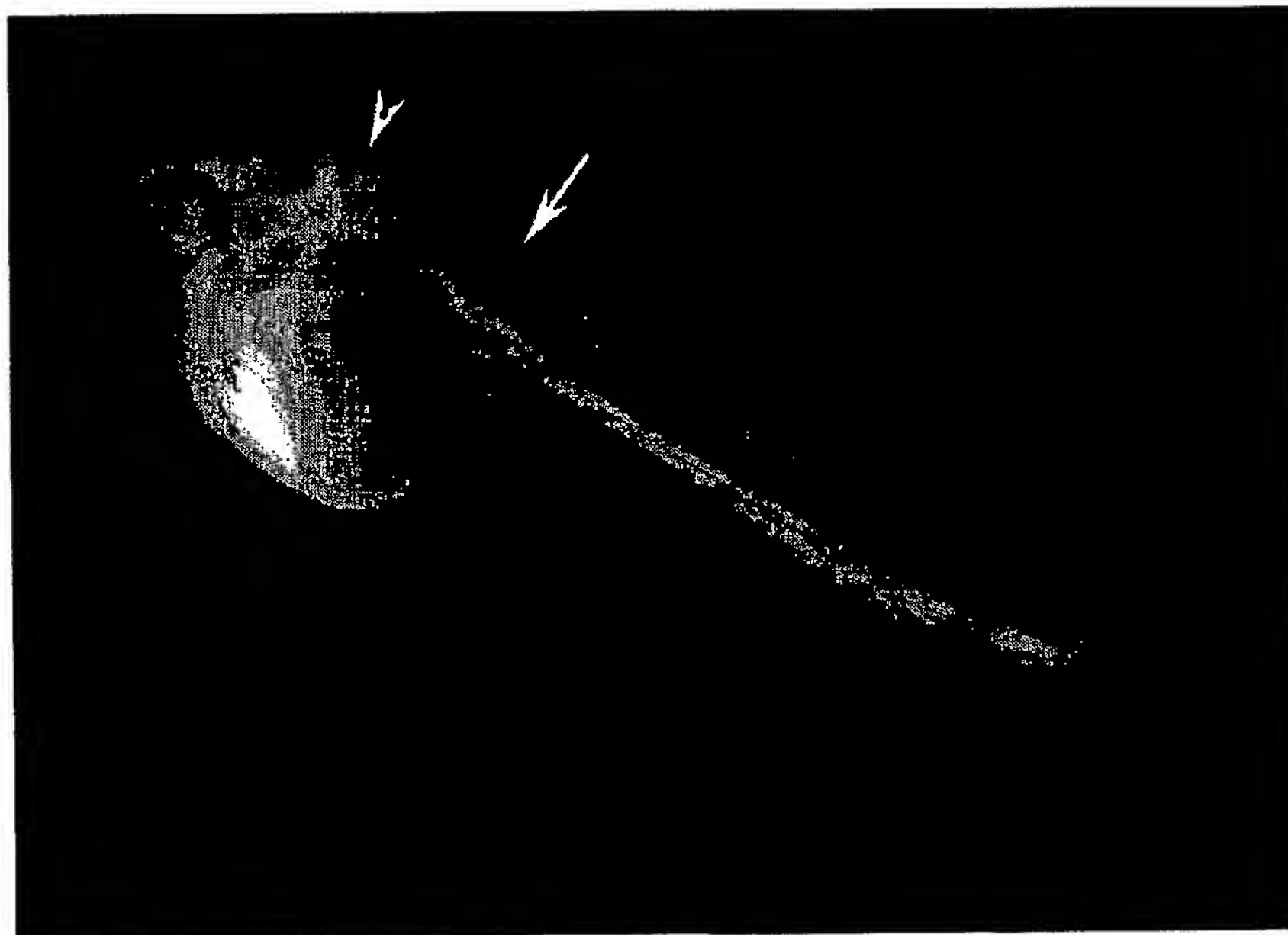


Figure 47

	Intensity	log2_exp_ratio	p-value	rank
ec/r	8,2	0,88		600
ec/lo	8,1	0,80		449
abeclo	7,6	0,60	1,00	
abecebec	8,3	0,27	0,76	
aheclo	7,3	1,17	1,00	
ebeclo	9,1	-0,29	0,23	
eheclo	8,1	1,21	1,00	
eseclo	8,1	-0,13	0,25	

Table 1: Expression profile data for gene HUP8001J6.

Probe	Number analysed	Results
<i>fli-1</i>	16	13%H
<i>flk-1</i>	15	7%H
<i>tie-1</i>	15	normal
<i>cdh5</i>	23	normal
<i>flt-4</i>	15	normal
<i>tie-2</i>	15	normal

Table 2: secondary *in situ* hybridization data

	Intensity	log2_exp_ratio	p-value	rank
ec/r	7,8	-0,11		6732
ec/lo	7,8	0,59		804
abeclo	7,9	3,52	1,00	
abecebec	8,4	2,10	1,00	
aheclo	7,5	-1,05	0,00	
ebeclo	8,8	2,15	1,00	
eheclo	7,5	-0,07	0,42	
Esaclo	7,5	-0,56	0,01	

Table 3: Expression profile data for gene HUP8001K17.

	Morphants with 1 ng sz143, 4 ng sz144		Morphants with 1.5 ng sz143, 6 ng sz144	
Probe	Number analyzed	Results	Number analyzed	Results
<i>fli-1</i>	17	6%M, 18%H	12	42%H
<i>flk-1</i>	15	20%M, 13%H	13	23%H
<i>tie-1</i>	16	63%H	13	54%H
<i>cdh5</i>	24	4%M, 4%H	27	15%M, 11%H
<i>flt-4</i>	13	normal	14	normal
<i>tie-2</i>	19	normal	18	normal

Table 4: secondary *in situ* hybridization data

	Intensity	log2 exp ratio	p-value	rank
eccl	8,5	0,88		594
eclo	8,4	0,80		442
abeclo	8,5	0,71	1,00	
abecbec	8,8	-0,02	0,48	
aheclo	8,0	1,15	1,00	
ebeclo	9,5	-0,03	0,47	
eheclo	8,3	0,72	0,98	
eseclo	8,3	0,49	0,99	

Table 5: Expression profile data for gene HUP8001K21.

Probe	Number analyzed	Results
<i>fli-1</i>	15	normal
<i>flk-1</i>	16	13%L, 6%H
<i>tie-1</i>	15	normal
<i>cdh5</i>	26	normal
<i>flt-4</i>	17	normal
<i>tie-2</i>	20	normal

Table 6: secondary *in situ* hybridization data

	Intensity	log2 exp ratio	p-value	rank
eccl	9,1	0,48		2061
eclo	9,0	1,30		149
abeclo	8,1	3,14	1,00	
abecbec	8,7	2,26	1,00	
aheclo	8,9	0,23	0,85	
ebeclo	9,1	0,51	0,90	
eheclo	9,5	1,32	1,00	
eseclo	9,0	1,84	1,00	

Table 7: Expression profile data for gene HUP8003D24

	Morphants with 3 ng sz185, 6 ng sz186		Morphants with 6 ng sz185, 12 ng sz186	
Probe	Number analyzed	Results	Number analyzed	Results
<i>fli-1</i>	11	18%M, 36%H	3	33%L, 33%M
<i>flk-1</i>	11	36%H	2	100%M
<i>tie-1</i>	14	29%H	n/a	no data
<i>cdh5</i>	16	31%M, 31%H	7	100%H
<i>flt-4</i>	16	normal	3	normal
<i>tie-2</i>	15	normal	7	normal

Table 8: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
eecl/r	9,0	1,12		262
ec/lo	9,0	0,75		516
abeclo	8,0	0,44	0,79	
abecebec	8,6	-0,80	0,03	
ahedlo	9,0	-0,47	0,02	
sbeclo	8,8	1,68	1,00	
ehedlo	9,3	1,18	1,00	
eseclo	9,0	1,22	1,00	

Table 9: Expression profile data for gene HUP8004N1

Probe	Number analyzed	Results
<i>fli-1</i>	15	7%L, 7%H
<i>flk-1</i>	14	7%H
<i>tie-1</i>	14	7%L, 7%H
<i>cdh5</i>	26	8%M
<i>flt-4</i>	15	normal
<i>tie-2</i>	15	normal

Table 10: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
eecl/r	8,8	0,98		424
ec/lo	8,7	0,36		1747
abeclo	8,4	0,26	0,63	
abecebec	8,2	-2,20	0,00	
ahedlo	8,4	-0,06	0,38	
sbeclo	8,7	0,72	0,95	
ehedlo	9,4	0,14	0,67	
eseclo	8,9	-0,37	0,03	

Table 11: Expression profile data for gene HUP8010A10

	Morphants with 4 ng sz267, 2 ng sz268		Morphants with 6 ng sz267, 3 ng sz268	
Probe	Number analyzed	Results	Number analyzed	Results
<i>fli-1</i>	15	13%H	16	25%L, 19%H
<i>flk-1</i>	15	33%L, 20%H	6	33%L
<i>tie-1</i>	17	normal	15	67%H
<i>cdh5</i>	25	8%H	24	21%L, 13%M, 29%H
<i>flt-4</i>	13	normal	15	normal
<i>tie-2</i>	16	normal	15	normal

Table 12: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
eecl	7,7	-0,06		6087
eclo	7,6	0,40		1547
abeclo	7,5	1,47	0,97	
abecabec	8,3	0,30	0,77	
aheclo	7,2	-0,04	0,41	
ebeclo	8,3	1,87	1,00	
eheclo	7,8	0,60	0,99	
esecl	7,5	-0,13	0,24	

Table 13: Expression profile data for gene NOC8003L17

Probe	Number analyzed	Results
<i>fli-1</i>	15	40%H
<i>flk-1</i>	7	normal
<i>tie-1</i>	15	normal
<i>cdh5</i>	20	15%L, 5%M, 30%H
<i>flt-4</i>	11	normal
<i>tie-2</i>	16	normal

Table 14: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
eecl	8,1	0,84		685
eclo	8,0	1,19		184
abeclo	7,4	1,57	1,00	
abecabec	8,1	1,44	1,00	
aheclo	8,4	0,12	0,74	
ebeclo	8,0	1,52	1,00	
eheclo	8,3	0,53	0,98	
esecl	7,9	2,41	1,00	

Table 15: Expression profile data for gene NOC8009C9

Probe	Number analyzed	Results
<i>fli-1</i>	15	7%M
<i>flk-1</i>	15	normal
<i>tie-1</i>	15	7%H
<i>cdh5</i>	20	15%L, 5%M, 15%H
<i>flt-4</i>	15	normal
<i>tie-2</i>	16	normal

Table 16: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
eccl/r	8,3	0,23		3262
ec/lo	8,2	1,19		185
abeclo	7,2	2,94	1,00	
abecabec	8,1	2,09	1,00	
ahaclo	8,0	1,15	1,00	
ebaclo	8,2	0,75	0,94	
ehaclo	9,0	-0,02	0,47	
esaclo	8,1	2,51	1,00	

Table 17: Expression profile data for gene NOC8009G23

	Morphants with 2 ng sz149, 2 ng sz150		Morphants with 3 ng sz149, 3 ng sz150	
Probe	Number analyzed	Results	Number analyzed	Results
<i>fli-1</i>	14	21%H	15	13%M, 27%H
<i>flk-1</i>	16	normal	15	7%L, 7%M, 20%H
<i>tie-1</i>	22	36%H	13	62%H
<i>cdh5</i>	15	13%L***	12	25%H***
<i>flt-4</i>	16	normal	15	13% low axial effects
<i>tie-2</i>	13	normal	8	normal

Table 18: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
eccl/r	8,1	0,67		1246
ec/lo	8,0	1,37		123
abeclo	7,1	2,90	1,00	
abecabec	8,1	0,59	0,92	
ahaclo	7,6	0,19	0,85	
ebaclo	8,7	1,41	1,00	
ehaclo	8,4	1,89	1,00	
esaclo	7,7	1,28	1,00	

Table 19: Expression profile data for gene OJC8003C9

	Morphants with 3 ng sz185, 6 ng sz186		Morphants with 6 ng sz185, 12 ng sz186	
Probe	Number analyzed	Results	Number analyzed	Results
<i>fli-1</i>	10	20%L, 10%M, 10%H	10	10%M, 50%H
<i>flk-1</i>	9	11%L, 33%M, 11%H	12	25%M, 25%H
<i>tie-1</i>	9	22%H	6	17%L, 50%H
<i>cdh5</i>	7	14%M, 14%H	5	40%M
<i>flt-4</i>	9	normal	9	normal
<i>tie-2</i>	7	normal	6	normal

Table 20: secondary *in situ* hybridization data

	intensity	log2 exp ratio	p-value	rank
sec/r	8,5	0,62		1445
ec/lo	8,3	1,03		257
abaclo	8,3	2,37	1,00	
abecebec	9,2	0,38	0,84	
ahaclo	7,9	0,93	1,00	
ebaclo	8,8	1,53	1,00	
ehaclo	8,8	1,03	1,00	
esaclo	8,5	0,48	0,99	

Table 21: Expression profile data for gene OJC8009J7

Probe	Number analyzed	Results
<i>fli-1</i>	14	7%L, 29%M
<i>flk-1</i>	12	25%L, 8%H
<i>tie-1</i>	9	11%M, 11%H
<i>cdh5</i>	16	19%L, 6%M, 19%H
<i>flt-4</i>	10	normal
<i>tie-2</i>	6	normal

Table 22: secondary *in situ* hybridization data